Supreme Court, U.S.
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No. _____

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In The
Supreme Court of the United States

ROY LEE LUNDY *et al.*,
Petitioners,
v.
AMERICAN CYANAMID COMPANY,
Respondent,

and

JOSEPH R. GRAHAM *et al.*,
Petitioners,
v.
AMERICAN CYANAMID COMPANY,
Respondent.

ON PETITION FOR WRIT OF CERTIORARI
TO THE UNITED STATES COURT OF APPEALS
FOR THE SIXTH CIRCUIT

PETITION FOR WRIT OF CERTIORARI

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QUESTION PRESENTED

Where a circuit court, in a case involving the violation of a federal statute, 42 U.S.C. § 262(d), and its implementing regulations, fails to apply and materially deviates from the controlling United States Supreme Court decision, Berkovitz v. United States, 486 U.S. 531 (1988), should not this Court grant a Writ of Certiorari to enforce the Congressional mandate, the regulatory process, and the rule of law enunciated by this Court?

PARTIES TO THE PROCEEDING IN THE SIXTH CIRCUIT

The parties to Graham v. American Cyanamid Company (No. C-2-94-423 in the district court and No. 01-4175 in the Sixth Circuit), were Joseph R. Graham and Lisa A. Graham, as individuals, and Joseph R. Graham and Lisa A. Graham, as parents and next friend of Zachary A. Graham (a minor at the time of filing the action), as plaintiffs, and American Cyanamid Company, as defendant.

The parties to Lundy v. American Cyanamid Company (No. C-2-94-425 in the district court and No. 01-4176 in the Sixth Circuit), were Roy Lee Lundy and Janet Lundy, as individuals, and Roy Lee Lundy and Janet Lundy as parents and next friend of Jason Lundy (a minor at the time of filing the action), as plaintiffs, and American Cyanamid Company, as defendant.

CORPORATE DISCLOSURE STATEMENT PURSUANT TO RULE 29.6

None of the parties plaintiff in the Graham and Lundy actions who seek *certiorari* is a corporate entity.

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PETITION FOR A WRIT OF CERTIORARI

Roy Lundy, his wife Janet Lundy, and his son, Jason Lundy respectfully seek a Writ of Certiorari to review the decision of the United States Court of Appeals for the Sixth Circuit, which, on December 3, 2003, affirmed a Summary Judgment Order and Judgment dismissing the action, issued by the United States District Court for the Southern District of Ohio, entered on December 21, 2001. In this same petition, Zachary Graham, his mother Lisa Graham, and his father Joseph Graham respectfully seek a Writ of Certiorari to review the same decision of the United States Court of Appeals for the Sixth Circuit, which affirmed a Summary Judgment Order and Judgment dismissing the action, issued by the United States District Court for the Southern District of Ohio, entered on December 21, 2001. The *Lundy* and *Graham* actions were decided in a single decision by the trial court; that decision in turn, was affirmed by the Sixth Circuit in one decision.

In the Lundy action, plaintiff Roy Lundy claimed that he contracted Type III paralytic poliomyelitis through contact with his recently-immunized infant son, Jason. The oral polio vaccine which was administered to his infant son had not been licensed, tested, and manufactured in accordance with the federal oral polio vaccine regulations. One of the particular batches of trivalent vaccine Jason may have received contained rejected and expired vaccine, as well as a monovalent pool that was more neurovirulent than the entire neurovirulence safety testing history of the reference standard as conducted by the manufacturer, Cyanamid.

In the Graham action, plaintiff Zachary Graham's parents claimed that their infant son contracted paralytic poliomyelitis after ingesting a dose of Orimune vaccine which was defective. The violations of the same federal regulatory scheme that was applicable to the

Lundy case was applicable to Zachary Graham's immunization. In both instances, the vaccine manufacturer failed to comply with the licensing, testing and manufacturing requirements for the vaccine at each stage of manufacture.

OPINIONS BELOW

The opinion of the Court of Appeals (App. A)[1] and Judgment (App. A at 31) is reported at 350 F.3d 496 (6th Cir. 2003). The unpublished opinion of the lower court is available at 2000 WL 1911431 (S.D.Ohio 2000, Dec. 21, 2001) (App. B). The Judgment of the District Court appealed from in Graham (App. B at 31), and in Lundy (App. B at 33) are unreported.

JURISDICTION

The jurisdiction of this Court is invoked pursuant to 28 U.S.C. § 1254(1).

STATUTES INVOLVED IN THE CASE

The statutes involved are 28 U.S.C. § 1254(1), Federal Rules of Civil Procedure Rule 56, and 42 U.S.C. § 262(d) (App. C). The regulations involved are the federal regulations governing live oral poliovirus vaccine, 42 C.F.R. Part 73, later re-numbered as 21 C.F.R. Part

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[1] References to the Appendices which are bound in this volume are preceded with the section designations "App. A," App. B." etc..

630. Relevant portions of those regulations are set forth in Appendix E.

STATEMENT OF THE CASE

Background

Since the introduction of oral polio vaccine in the United States in 1962 until its removal from sale in 1999, American Cyanamid/Lederle has been America's major supplier of Sabin Oral Poliovirus Vaccine. Beginning in 1962, when it first applied for its license, until 1977, American Cyanamid/Lederle had approximately 83% of the United States market. After 1977, it was the sole oral poliovaccine manufacturer in the United States until 1999, when Orimune was no longer recommended for pediatric immunization. At all times relevant to this petition, a completely safe alternative vaccine, the Salk vaccine, also known as inactivated polio vaccine ("IPV"), was available to the American public.[2]

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[2] In 1977, the Institutes of Medicine issued a report known as the Nightingale Report, which found there was no benefit to the individual recipient of oral polio vaccine over immunization with inactivated polio vaccine. Cf. Lundy v. American Cyanamid Company, 350 F.3d at 499. The Sixth Circuit's recitation of the properties of IPV and OPV and their differences is historically inaccurate and conflicts with both the Institutes of Medicine Report written in 1977, *The Institutes of Medicine Evaluation of Poliomyelitis Vaccines, The Nightingale Report,* IOM Publication 77-02, and all other scientifically correct descriptions, as can be found in the manufacturer's own package insert beginning in the late 1980's.

Between 1979 and 1999, the *sole* source of paralytic poliomyelitis cases in the United States was the oral polio vaccine known as "Orimune," the vaccine product manufactured by American Cyanamid Company / Lederle Laboratories. Once the nation's pediatric regimen was changed from oral polio vaccine to inactivated polio vaccine in 2000, not a single child or adult in the United States was thereafter afflicted with paralytic poliomyelitis, and no wild cases of polio have occurred.

The Roles of the Division of Biologics Standards and the National Institutes of Health in Regulating Oral Poliovirus Vaccine.

Oral poliovirus vaccine, as every other vaccine utilized to immunize the population in order to protect the public health of the United States, was initially regulated not by the Food and Drug Administration (FDA), but by the Division of Biologics Standards (DBS), part of the United States Public Health Service. The FDA did not assume any responsibility for vaccines until 1972, when the DBS was found liable for releasing non-compliant oral polio vaccine. Griffin v. United States 351 F. Supp. 10 (E.D. Pa. 1972), aff'd, 500 F.2d 1059 (3d Cir. 1974).

Poliovirus was a scourge to humans because of its capability to attack the nervous system and permanently destroy the capacity of particular nerve cells to relay through the spinal cord the electrical potentials which activate muscles. Thus, when public health officials geared up for use of a live virus vaccine in the United States, they proposed and adopted a set of highly detailed and stringent regulations which had as their goal to implement the best methods then known to science to insure that the neurovirulence of manufac-

tured vaccine would be at an acceptably safe level. To accomplish this goal, they specified a particular licensing, manufacture, and safety testing regimen from which manufacturers *could not diverge* if they wished to sell OPV.

Lederle was one of only a handful of biologics manufacturers that decided to apply for an OPV license. During the period of American Cyanamid's licensure, it and each of the other license applicants were required to submit to the government the test results demonstrating -- *as a condition precedent to subsequent lawful manufacture of polio vaccine* -- that its master seeds, production seeds, and/or intermediate seeds passed all regulatory safety requirements *and* that the manufacturer's test results for the *final product*, in the form in which it distributed it, *also demonstrated* that that product fully complied with the regulations.

The record below demonstrated that Cyanamid did not perform the necessary tests and did not submit any seed test results with its Orimune license applications. Moreover, the consistent uncontradicted record testimony of Cyanamid's personnel is that the vaccine manufacturer *did not* submit the test results. The vaccine manufacturer did not submit the test results for two reasons: first, most of the test results, had they been submitted, would have shown the applicant's failure to comply with the regulations then in effect, such as that all of its seeds were contaminated with an adventitious agent (i.e., one from an extrinsic source) known as SV40, which had been shown to cause cancer in test animals and whose presence in the vaccine was prohibited explicitly by regulation. 42 C.F.R. § 73.110(b)(3). Cyanamid had *not* demonstrated that it had successfully tested for *and removed* the SV40, a specific requirement for licensure pursuant to

this Court's Berkovitz opinion. Second, no tests were submitted for neurovirulence (see 42 CFR §§ 73.110(b)(2)(ii), 73.110(b)(4), 73.114(b)(1) (Supp. 1964); 21 CFR §§ 630.110(b)(2)(ii), 630.110(b)(4), 630.16(b)(1) (1987)) (App. D) or markers (42 C.F.R. § 73.114(3)(i), (ii), (iii)), for any of the seeds utilized to license this oral poliovaccine product. The adventitious agent test results were not submitted for *any* of the seeds utilized to license this product. See 42 C.F.R. §§ 73.110 (b)(3), and 73.112, 113 and 114.

What testing *was* conducted, and what records do exist in regard to neurovirulence and markers, proved that both the licensing lots and the subsequent lots manufactured for distribution exceeded the neurovirulence safety requirements and were more neurovirulent than the "reference standard," a vaccine provided to manufacturers by which safety testing results could be calibrated to a standard for maximally permissible acceptable neurovirulence. 42 C.F.R. §§ 73.114(b)(1)(iii); In re Sabin, infra, 763 F. Supp. at 815-817, 826-827, 829.

Throughout the years Orimune was produced, American Cyanamid/Lederle assured the courts, the public, the medical profession, the state legislatures, and all others that it warranted that it had **fully complied** with each and every regulation in effect at each relevant time period. This promise and guarantee of compliance, prominently displayed in each of Cyanamid's Orimune advertisements, package inserts, and vaccine containers, was false. One of respondent's managers, who was in charge of communications with physicians, admitted that no physician would use a non-licensed vaccine and, more importantly, no vaccine manufacturer could *or should* be able to sell an unlicensed product.

During all times relevant herein, the regulations that were enacted in 1960 remained in full effect at the time that Roy Lundy, one of the petitioners herein, was paralyzed through contact with his recently immunized infant son, Jason, and when petitioner Zachary Graham, then a minor, was paralyzed by ingesting Orimune.

Roy Lundy

Roy Lundy is a wheelchair-bound contact polio victim of Type III poliovirus from Orimune which contained a neurovirulent component which exceeded the entire reference history of Lederle's safety testing in comparison to the reference standard from 1962 to 1977, and thereafter, until 1999. One of the trivalent bulks that could have been administered to Roy's son Jason came from rejected, expired vaccine, *without knowledge of or permission from the FDA.* Sale of such vaccine was strictly prohibited by the applicable regulations at the time Jason Lundy was vaccinated.

Zachary Graham

Zachary Graham is a lower-limb paralyzed direct recipient case of paralytic poliomyelitis. His case was evaluated by the Centers for Disease Control, and he was determined to be a vaccine-associated case of polio. There are no test results showing that the various seeds utilized in manufacture of Zachary's final production seed passed all the required safety tests and, specifically, neurovirulence and marker tests, which, by regulation, are utilized to judge the safety of the vaccine prior to release. It was admitted below that the vaccine was

beyond five tissue culture passages. Pursuant to the In re Sabin decision (763 F. Supp. at 813, 821 823), this Court's Berkovitz decision (486 U.S. at 541, 544, 545 n.11), and the regulations then in effect (42 C.F.R. § 73.113(b)), Zachary Graham's vaccine could not legally be sold.

PROCEEDINGS BELOW

Following several years of consolidated pretrial discovery in Graham and Lundy, in 1998 American Cyanamid filed two summary judgment motions. It sought to dismiss Jason Lundy's product defect, negligence, breach of express warranty, and fraud claims and the dismissal of Roy Lundy's fraud and punitive damages claim. Plaintiffs opposed the motions. The district court granted summary judgment on both motions on December 21, 2000, finding that defendant was entitled to summary judgment. Plaintiffs moved to amend judgment, which the court denied on September 28, 2001.

On the same day, Cyanamid filed parallel motions in Graham. Plaintiffs opposed them. The district court granted summary judgment on both motions on December 21, 2000. Plaintiffs moved to amend judgment, which the court denied on September 28, 2001.

Plaintiffs in both cases timely appealed. The Sixth Circuit affirmed the lower court, finding that

violation of licensing requirements and excessive vaccine neurovirulence did not cause the plaintiffs' paralysis. The plaintiffs in each case then petitioned this Court for certiorari.

REASONS FOR GRANTING THE WRIT

I. UNLESS AND UNTIL BERKOVITZ IS OVERRULED, THE SIXTH CIRCUIT'S AFFIRMANCE OF THE LOWER COURT CREATES AN IRRECONCILABLE CONFLICT WITH THIS COURT'S CONTROLLING ARTICULATION OF THE LAW.

Berkovitz v. United States, 486 U.S. 531 (1988), presented to this Court a polio victim's claims against the United States, as licensor of the instant defendant, American Cyanamid Company, for non-compliant manufacture of Orimune live oral polio vaccine. In the district court action, the Western District of Pennsylvania had denied the government's motion to dismiss on discretionary function exception grounds, and the government appealed. In Berkovitz v. United States, 822 F.2d 1322 (3d Cir. 1987), the Court of Appeals correctly held that "[T]he duty to submit test data rests with the manufacturer.", (the point of error which Petitioners address to the Court in Lundy and Graham), citing 21 C.F.R. §§ 601.2, 610.1, 630.10(b)(4) (822 F.2d at 1330, n.6), but reversed the lower court's additional finding that the government was also liable. The Third Circuit based its reversal upon the discretionary function exception to the Tort Claims Act, 28 U.S.C. §§ 1346(b) and 2680(a).

The Third Circuit's opinion stated: "It is therefore evident that looking at the [poliovirus vaccine] regulations as a whole, it is the manufacturer that is required

to perform the tests [set out in 42 C.F.R. §§ 73.114(b), 73.115, 73.117]." 822 F.2d at 1330 (emphasis supplied).

Judge Higginbotham's dissent, relying upon Baker v. United States, 817 F.2d 560 (9th Cir. 1987), and Loge v. United States, 662 F.2d 1268 (8th Cir. 1981), cert. denied, 456 U.S. 944 (1982), found that an additional and co-equal liability resided in the government. In language which was consistent with what this Court ultimately held, Judge Higginbotham agreed with his brethren as to the vaccine manufacturer, stating: "The regulations in this field **place mandatory duties upon a drug manufacturer, such as Lederle**, that seeks to obtain a federal license to market its drug product." 822 F.2d at 1332 (emphasis supplied). However, citing to the various regulatory requirements of 21 C.F.R. §§ 601.2(a), 630.10(b)(2), 630.10(b)(4), and 42 U.S.C. 262(d), he went further than the majority, adopting the position that the relevant statutes and regulations not only obligated Lederle, the licensee-applicant, to submit everything the regulations required, but also obligated the DBS to require submission of test results and review the same to measure whether there is full compliance. Id. at 1333.

Denial of a license when test data failed to prove that the vaccine conformed with the mandatory requirements -- which *were* the only applicable safety standards – was what this Court demanded. See 486 U.S. at 544, n.10, 548. If the manufacturer failed to submit the test results, the regulatory language imposed a non-discretionary duty on the regulator to **insure** that that manufacturer had to be properly licensed to manufacture its vaccine. One hundred percent compliance was required.

This Court reversed the Third Circuit and referenced with approval the broader reading of the

regulations articulated by the Eighth and Ninth Circuits, announcing what was assuredly intended to be the rule of law in regard to licensing and manufacture of all vaccines. The unanimous Supreme Court in Berkovitz, supra, stated:

> Under federal law, a manufacturer must receive a product license prior to marketing a brand of live oral polio vaccine. *See* 58 Stat. 702, as amended, 42 U.S.C. § 262(a). In order to become eligible for such a license, a manufacturer must first make a sample of the vaccine product. *See* 42 CFR § 73.3 (Supp. 1964); 21 CFR § 601.2 (1987). [FN7] This process begins with the selection of an original virus strain. The manufacturer grows a seed virus from this strain; the seed virus is then used to produce monopools, portions of which are combined to form the consumer-level product. Federal regulations set forth safety criteria for the original strain, *see* 42 CFR § 73.110(B)(2) (Supp. 1964); 21 CFR § 630.10(b)(2)(1987), the seed virus, seed 42 CFR § 73.110(b)(3), (4) (Supp. 1964); 21 CFR § 630.10(b)(3), (4) (1987), and the vaccine monopools, *see* 42 CFR § 73.114 (Supp. 1964); 21 CFR § 630.16 (1987).

Berkovitz v. United States, 486 U.S. at 541 (footnote omitted).

Notwithstanding Berkovitz, the Sixth Circuit in the within matter found that there *had* been non-compliance with the licensing regulatory demands, but nevertheless, equated its proximate cause significance to

that of an individual who does not have a driver's license at the particular moment of an accident leading to injury, but who had a valid driver's license the day before the accident, and could get one the day after the accident.

> The Grahams also claim that the Orimune vaccine Zachary received was defective because American Cyanamid was not properly licensed to manufacture it. While they question whether certain testing procedures necessary for licensing occurred, they offer no evidence that the company did not in fact have a valid license to manufacture Orimune. As with their other claims, they also offer no evidence that any anomalies in American Cyanamid's license proximately caused Zachary's injuries. In Ohio, the absence of a valid or properly issued license does not by itself establish the proximate cause of an injury. *Cf. Gulla v. Straus*, 154 Ohio St. 193, 93 N.E.2d 662, 664 (1950).

What the Sixth Circuit clearly misunderstood and failed to appreciate was the significance of the licensing requirements of *vaccines in particular*, a biological product which was mandated by many state legislatures to be administered to children throughout their early childhood years as a condition precedent to attending school. No legislator, physician, or public health official would have permitted the use of non-compliant or non-licensed vaccine. Stephen A. Szumski, Ph.D., was the associate director of Cyanamid's Professional Medical Service Department from 1965 to 1982. While employed in that capacity, he chaired a Cyanamid committee which had the authority over the wording of Orimune's

package inserts and the Physician's Desk Reference annual insert. The testimony of this witness was relied upon by the New Jersey Appellate Division in reversing a lower court grant of summary judgment for Cyanamid on theories of failure to warn, strict liability, negligence, fraud, and punitive damages in Campagna v. American Cyanamid Company, 337 N.J.Super. 530, 767 A.2d 996 (2001):

> Dr. Szumski was also asked if he was aware that defendant's vaccine had failed certain safety tests (tests that were required under the federal regulations), would he have "notified the medical profession" if the medical profession had asked whether the vaccine could be administered? Dr. Szumski answered, "Well, I certainly would have told them not to use it."
>
> The plaintiff's attorney then read to Dr. Szumski the disputed warning statement concerning regulatory compliance from the package insert and Dr. Szumski testified that he thought physicians would believe that statement. When asked if the statement would constitute a "misrepresentation" or "lie" if defendant had released vaccine that did not comply with the regulations, Dr. Szumski replied, "Well, if they [defendant] say so and it wasn't so, then certainly I would believe it's a lie."
>
> On cross-examination by defendant's attorney, Dr. Szumski was asked "[i]f it was determined by the [FDA] that a

technical violation of the regulations had no effect on the safety of the [Orimune OPV] vaccine, do you think it would be reasonable for [defendant] to rely on that?" Dr. Szumski answered, "Yes, [defendant] would take action and they probably wouldn't market it." Unsatisfied with this answer, defendant's attorney repeated the question and Dr. Szumski again replied: "[Defendant] would probably act on it [the FDA's determination] and not use the vaccine." Still unsatisfied, defendant's attorney repeated the question again, whereupon Dr. Szumski answered that defendant "would use their judgment" in relying on the FDA's determination.

Finally, on redirect examination by the plaintiff's attorney, Dr. Szumski was asked, "Doctor, if in 1978 [Orimune OPV] did not technically comply with the regulations, if you were aware of that in 1978, would you have informed physicians, hospitals, and other health care providers of that fact?" Defendant's attorney objected, and the plaintiff's attorney rephrased the question, asking "If it [Orimune OPV] did not technically comply with the regulations in 1978, would you have informed health care providers of that fact?" Dr. Szumski replied that, "[i]f it didn't comply with the regulations, it wouldn't have been on the market."

Id. ,767 A.2d at 545-547.

It is evident that this Court's holding in Berkovitz

was disregarded by the Sixth Circuit when it reviewed the Graham and Lundy appeals. This Court necessarily and implicitly ruled that if a vaccine manufacturer fails to submit any of the requisite safety tests of its license application, *it cannot sell the product.* If the manufacturer succeeds in obtaining licensure because of the regulator's failure to enforce regulatory requirements, neither the government nor the vaccine manufacturer can claim that a person injured does not have a valid damage claim. Any conduct which departs from what the regulations mandate is squarely prohibited. If the manufacturer-license applicant fails to submit the required safety test results, or if the sample of the oral polio vaccine product intended to be marketed fails the government's own safety testing, or if the manufacturer failed to present proof as to the absence of adventitious agents, then the license application as presented **must be rejected**. Pursuant to the Public Health Service Act, 42 U.S.C. § 262(d), and the regulations enacted thereunder, neither the government *nor the vaccine maker* can permit the product to be sold. The Berkovitz Court held:

> A regulation similarly provides that "[a] product license shall be issued only upon examination of the product and upon a determination that the product complies with the standards prescribed in the regulations . . . ." 42 CFR § 73.5(a)(Supp. 1964); *see* 21 CFR § 601.4 (1987). In addition, a regulation states that "[a]n application for license shall not be considered as filed" until the DBS receives the information and data regarding the product that the manufacturer is required to submit. 42 CFR § 73.3 (Supp. 1964); 21 CFR § 601.2 (1987). These statutory and

> regulatory provisions require the DBS, prior to issuing a product license, to receive **all data the manufacturer is required to submit**, to examine the product, and to make a determination that the product complies with safety standards.

Berkovitz, 486 U.S. at 542 (emphasis supplied).

It is unquestionable that from the very earliest days of Orimune, American Cyanamid fully understood the importance of compliance with the regulations: in order to convince physicians, legislators, the parents of infants, and the public health community that its vaccine was safe, Lederle stated on each of its package inserts, and on each container of Orimune that was shipped from its plant, that it had *fully complied with all of the regulations that were in effect at the time of release.* See Lundy & Graham v. American Cyanamid Company, 2000 WL 1911431 at *5 (App. B). That express and affirmative warranty statement was false (see In Re Sabin Oral Polio Vaccine Products Liability Litigation, 984 F.2d 124 (4th Cir. 1993), aff'g 743 F. Supp. 410 (D. Md. 1990) ("Sabin I"), 763 F. Supp. 811 (D. Md. 1991) ("Sabin II"), and 774 F. Supp. 952 (D. Md. 1991) ("Sabin III")) and flew directly in the face of what the vaccine manufacturer was required to do under the Public Health Act and under the regulations which were enacted pursuant to that Congressional mandate.

Berkovitz v. United States is the law of the land, and if this Court fails to grant certiorari, the Sixth Circuit's decision in these cases will conflict irreconcilably both with this Court's Berkovitz decision and the decisions of the circuits which have applied Berkovitz' holdings and with the applicable federal

statute, 42 U.S.C. § 262(d), not to mention the plain meaning of the text of the regulations themselves. In essence, the requirement to be properly licensed in order to sell a vaccine (or, in a more general sense, a drug) in the United States, which was the basis for this Court's discretionary function exception decision in Berkovitz, will have been abolished by the Sixth Circuit, notwithstanding the clear language of this Court and the authorizing statutes.

The possibly unintended but inevitable consequence of allowing the Lundy and Graham decision to stand will be that in the future, a drug or vaccine manufacturer will be able to point to the Sixth Circuit decision and argue that whenever licensing requirements may have been overlooked, ignored, omitted, performed improperly, *or even falsified* and resulted in injury or death, *the government,* and not the manufacturer / licensee, is liable in damages for breach of that duty, and that Berkovitz, supra, does not in any way speak to liability which can result from failures or defalcations on the part of the manufacturer.

To the contrary, Berkovitz confirmed that a regulatory system such as that which governed the oral polio vaccine involved here created a very calculated and deliberate additional layer of liability, over and above *the vaccine manufacturer's direct liability, which has never been diminished by this Court.* Furthermore, in the face of the oral polio regulatory scheme, *that direct liability was strict and absolute if the regulation was breached at any time or at any juncture. The failure of experts to cite peer-viewed studies to support their conclusions where there are unquestioned violations of the safety tests used to measure neurovirulence of the vaccine cannot be a basis to deny relief to paralyzed polio victims exposed to an unacceptably neurovirulent vaccine.*

Cyanamid's failure to submit the safety test results can not be as the Sixth Circuit has determined -- that it is "only an issue of licensing" and, therefore, not important, much as failure to have a driver license is not a basis for liability in Ohio.

Clearly, from the Pennsylvania District Court and Third Circuit decisions which were the predicate of what this Court ruled in Berkovitz, *it was a given* that the regulations at issue were addressed to the conduct of the manufacturer and governed the conduct of the manufacturer with *at least as great consequence in their breach* as attached to the government. This Court in Berkovitz did not alter in any manner that portion of the two Berkovitz decisions below which correctly articulated the law as it applied to the vaccine manufacturer.

Petitioners respectfully submit that if that is the case, and if Berkovitz v. United States is to have any substantive meaning at all, this Court must re-affirm what it cogently proclaimed in Berkovitz , but the Sixth Circuit declined to accept: the obligation of the vaccine manufacturer, as well as the government, must fulfill the duties created and mandated by the duly promulgated regulatory system *in effect at the time of the release of the product*, which system had been subject to extensive public and industry comment.

For this reason, we respectfully request this Court to grant the Writ of Certiorari so that this issue involving the duties of drug and vaccine manufacturers to comply under the federal regulations can be clarified for all time in regard to the licensing of this product.

A. Although Oral Polio Vaccine Is No Longer in Use in the United States, the Issues Raised by this Petition Are Not Moot, and the Issue of the Safety of this Vaccine Is a Matter of National Concern to the Public Health.

The mootness doctrine does not apply here and is not an appropriate reason for the Court to deny certiorari in these cases. To the contrary, the extreme currency and the high importance of the Court's review of this matter can easily be ascertained by examining the Orimune-related public health issues *currently* being discussed and debated in the scientific community and in its peer-reviewed literature as a new public health issue of substantial concern. That issue is whether Orimune oral polio vaccine contained the carcinogenic simian virus adventitious agent, SV40, in violation of licensing provisions of the regulations which prohibited American Cyanamid from selling *any* Orimune which contained *any* adventitious agents. 42 C.F.R. § 73.110(b)(3) (renumbered as 21 C.F.R. § 630.10(b)(3)) (App. D). There is presently litigation in the courts of California, New Jersey, and Texas which questions whether American Cyanamid truthfully told the world scientific community that its Orimune product was free of the cancer-causing agent SV40. The failure to comply with the licensing requirements mandating demonstrative proof that SV40 was not in any oral polio vaccine intended to be distributed and sold in the United States is now before those courts, before the international scientific community, and before Congress.[3]

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[3] See Sept. 10, 2003: Hearing Before the House Energy and Commerce Subcommittee on Human Rights and Wellness, Com-mittee on Government Reform, Serial No. 108-85, *"SV-40 Virus: Has Tainted Polio Vaccine Caused An Increase in Cancer"* (available full text at www.access.gpo.gov/congress/house/

B. The Regulatory Scheme And The Amendments Thereto.

When Messrs. Lundy and Graham were paralyzed by the live virus in Orimune, the OPV regulations then in effect were basically the regulations that had been enacted in 1960. Those very regulations had been the subject matter of federal court decisions in Baker v. United States, 817 F.2d 560, 566 (9th Cir. 1987) (license may not issue unless vaccine manufacturer has submitted *all* the relevant test data), Berkovitz, and Loge v. United States, 662 F.2d 1268 (8th Cir. 1981), cert. denied, 456 U.S. 944 (1982), and thereafter, the In Re Sabin decisions cited supra. In 1991, following the District Court's decisions in In Re Sabin ("Sabin II"), the United States, at the behest of American Cyanamid, immediately changed the regulations to permit the legal sale of Orimune at a tissue culture passage greater than the five tissue culture passages the regulations had

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house07ch108.html (accessed 02/28/04); Hearing Before the House Energy and Commerce Subcommittee on Human Rights and Wellness, Committee on Government Reform, Nov. 13, 2003: *"Preventing Another SV40 Tragedy: Are Today's Vaccine Safety Protocols Effective?"* Serial No. ___ (in press); Report by Immunization Safety Review Committee on Health Promotion and Disease Prevention of the Institute of Medicine, *Immunization Safety Review SV40 Contamination of Polio Vaccine and Cancer*; Klein G, Powers A, Croce C. *"Association of SV40 with human tumors"* Oncogene, 21:1141-1149, 2002; Gazdar, A.F., Butel, J., and Carbone, M.,*SV40 virus and human tumours*, Nature Reviews Cancer, 2:957-964, 2002. *Cf.* American Cyanamid's presentation and paper by Brock, Kelleher and Zlotnick: Simian Virus 40 (SV40): A Possible Human Polyomavirus: Product Quality Control testing for the Oral Polio Vaccine, Developments, *Biologic Standardization*, 217-219 (1998).

previously permitted.

At Cyanamid's request following Sabin II, supra, the government re-designated what the "original strain material" would be considered to be for the Type III component of the trivalent vaccine. At that time and for many years before, the only OPV manufacturer in the United States was American Cyanamid, and the only oral polio vaccine sold was Orimune. American Cyanamid by that time realized that it could no longer utilize the seeds that it had been utilizing to produce its Type III trivalent component, because they had been shown to be highly neurovirulent in humans, and the Maryland District Court and the Fourth Circuit had so held. See In Re Sabin, supra, 763 F. Supp. at 817, 823 n.11, 827, 828, citing Berkovitz (at 827). See also Berkovitz, supra, 486 U.S. at 547.

Even after the regulations were changed in 1991, that change, relating to tissue culture passages, pertained **solely** to the Type III component; the regulatory agency was not asked to make changes to any other parts of the regulations, and it did not do so sua sponte. Accordingly, the Type I and Type II components, which were combined with the Type III to make the trivalent Orimune vaccine Jason Lundy and Zachary Graham received, all had to have passed the requirements of the mandatory regulatory system. Not a single type[4] of polio vaccine ever satisfied the initial licensing requirements which were in effect in 1991 and which

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[4] There are three strains of wild poliovirus and, therefore, three types of vaccine are needed to confer human immunity. Shortly after introducing Orimune as three different monovalent vaccines, Cyanamid applied for and received permission to market a trivalent product, the only form of Orimune thereafter sold.

remain in effect even today (see POINT III, infra), and *the failure to submit the test results of all seeds continued with respect to the Type I and Type II vaccines utilized in the United States from the 1970s to 1999*, when the last oral polio vaccine was distributed in the United States. American Cyanamid has been forced to admit to the same, and it is part of the Congressional record. Sept. 10, 2003 Hearing, Report Serial No. 108-85, at 231-232 (Request for Admissions Nos. 9 and 10).

The 1991 change in regulations did no more than make **prospectively** permissible and "acceptable" under the amended regulations a Type III vaccine component that was at the seventh tissue culture passage from the original seed. If, for example, Zachary Graham had been a plaintiff in the In Re Sabin Multi District Litigation, he would have been entitled to judgment either against the United States **or against American Cyanamid, just as were the actual In Re Sabin plaintiffs,** in whose favor judgment was entered and affirmed, because Zachary's paralysis had occurred prior to 1991.

The subsequent removal of the regulations in 1996 (see 350 F.3d at 514) pertained to *all vaccines*, not merely oral poliovirus vaccine. In any event, it was unrelated to *the initial licensing requirements applicable to every manufacturer-applicant* for a vaccine license. This change indicated that the regulator, in order to fulfill the congressional mandate, agreed with this Court and its holding that the license and the tests conducted to procure that license *was* the measuring rod used to determine the safety of the product. The word *standard* was further defined in 1996 to constitute " . . . specifications and procedures applicable to an establishment or to the manufacture or release of products, which are prescribed in this subchapter **or established in the biologics license application**

designed to insure the continued safety, purity and potency of such products." 21 C.F.R § 600.3(n) (2000) (emphasis supplied). The regulations were still to be followed, because the license requirements demanded it. *From 1996 until the last day on which it manufactured Orimune, American Cyanamid continued the identical test regimen it had used to produce the Lundy and Graham doses.* The requirements remained the same -- notwithstanding what the Sixth Circuit erroneously stated -- both in the statutory scheme and in actual practice.

II. THIS COURT SHOULD GRANT THE PETITION BECAUSE THE HOLDING OF THE SIXTH CIRCUIT DENIGRATES INTO OBLIVION NEUROVIRULENCE, THE CENTRAL UNDERPINNING OF THE ENTIRE FEDERAL OPV REGULATORY SCHEME.

The Sixth Circuit incongruously determined that notwithstanding American Cyanamid's failure to comply with the neurovirulence test standards (In re Sabin, 763 F. Supp. at 813, 815, 817 n.7, 818, 820, 822, 826, 827, 828 n.17, 829), and even though the neurovirulence of the vaccine was higher than the reference standard allowed, the Sixth Circuit stated that **that** did not relate to an increase in the risk to an individual recipient. 350 F.3d at 509-510, 511-512. The Sixth Circuit quoted this Court in part (350F.3d at 510), but failed to follow and apply *the entire statement* of this Court. The Sixth Circuit quoted the first sentence of this Court's description of neurovirulence, but then completely ignored and omitted the Court's next statement, which was that neurovirulence is the barometer by which one can determine whether administration of the vaccine will

result in vaccinees contracting paralytic poliomyelitis.

This Court stated the following in regard to neurovirulence:

> Neurovirulence is the capacity of an infectious agent to produce pathologic effects on the central nervous system. In this context, it refers to the vaccine's ability to cause paralytic poliomyelitis. The neurovirulence of a vaccine product is tested by injecting the product into monkeys. The product meets the neurovirulence criterion only if a specified number of the animals survive and a "comparative analysis" demonstrates that the neurovirulence of the vaccine product "does not exceed" the neurovirulence of a reference product previously selected by the agency. 42 CFR §73.114(b)(1)(iii) (Supp.1964); 21 CFR § 630.16(b)(1)(iii) (1987).

Berkovitz, supra, 486 U.S. at 542.

Such a position is irreconcilable under the plain language of the regulations and under the holding of Berkovitz v. United States, because the inescapable and anomalous conclusion which the Sixth Circuit's findings compel is that **there was no purpose served by the regulations.** See Report, Serial No. 108-85, supra, at 228-233, 240, 248.

As the record below amply demonstrated from Cyanamid's own business records (Cyanamid filings in FDA Docket No. 86N-0027, the public record of a formal rulemaking), the so-called "change" in the tests that occurred in 1991 (56 Fed. Reg. 21,418 et seq. (May 8,

1991)), had been fought by American Cyanamid in *at least seven separate submittals* to the FDA extending from 1984 through and after 1991. FDA Docket No. 86N-0027 (pertinent portions reproduced in App. E) reflects not the support for amendment "relaxing" the regulatory requirements, as one would anticipate from the position Cyanamid took in the court below, but rather the total **opposition** of the defendant below to any government attempt to amend the neurovirulence test protocol to broaden the range of test results which the regulations would accept as associated with a "safe" lot of vaccine. Cyanamid adopted this position notwithstanding that every FDA scientist involved in the rulemaking effort had concluded that the newer method of calculating the test results was *a better method of insuring public safety.* The In Re Sabin Court determined the following in 1991 in regard to American Cyanamid's willingness to utilize the new and safer method:

> In 1986 DBS did seek extensive amendments for the purpose of adopting the WHO regulatory scheme in the United States. Under the WHO regulations (of which, incidentally, Dr. Elisberg is a strong proponent) only intraspinal need to be conducted and type 3 lots are to be compared to a type 3 reference history. Opposed by Lederle, the proposed amendments failed.

763 F. Supp. at 821 n.10.

In the new test protocol proposed by the FDA and opposed by Cyanamid, the test performed was identical to what it had been, as was the degree (scored on a 0 - 4 "grade" scale) of any observed simian test animal

lesion, as was the method by which the calculation was to be performed. The only difference lay in what reference standard would be used, how one would compare the test results, and on what materials the tests would be conducted.

At the behest of American Cyanamid, however, the regulations ultimately **continued to allow** the vaccine manufacturer (in this instance, American Cyanamid, which had already assumed OPV monopoly-supplier status) to utilize none other than the identical method it had utilized from 1960 up to that point. After 1977, when the last of the OPV licensees competing with Lederle closed up shop under the intense economic pressure that Lederle's methods of marketing to pediatricians and other physicians created, no other vaccine manufacturer ever again sought licensure in the United States for the production of oral polio vaccine.

By preserving the regulations to require both the intrathalamic *and* intraspinal tests be conducted, as originally set forth in the regulations, Lederle realized its goal of excluding other biological firms from OPV market competition. The only other manufacturer did not perform the intrathalamic test. Lederle now had the best of all worlds: it would continue to present regulatorily-unacceptable vaccine lots to the releasing agency, and if they were approved for release -- whether rightly or wrongly -- that simply translated into that much more sellable product and profit for Cyanamid.

It was, in fact, precisely that wrongful approval under Berkovitz which resulted in the government being held liable by the Fourth Circuit in the In Re Sabin Multi District Litigation. See 984 F.2d 124, 128 (4th Cir. 1993).

By 1991, American Cyanamid knew from its lengthy production experience history that it could not comply with the new amendments were the government to enforce them, and conversely, that its competition, Connaught Laboratories, could not comply with the existing regulations, which the government was failing to enforce against Cyanamid. Therefore, by fighting any change until 1991, American Cyanamid accomplished its goal of keeping the competition out, while retaining the opportunity provided by government non-enforcement to continue to violate the neurovirulence regulations through monovalent pool test results that exceeded the entire history of testing on the reference standard. Cyanamid had convinced the FDA by that late date in American production of OPV that if the government would suddenly begin enforcing the regulations as the words of the regulation required, the results from the vaccine production of the nation's only OPV supplier would constitute an admission that the government had been violating, and continued to violate, the requirements this Court set out in Berkovitz.

III. THE POLIO VACCINE REGULATIONS HAVE NOT BEEN ABOLISHED.

The Sixth Circuit and the district court both found that the "removal" of all safety regulations in 1996 proved the contention of American Cyanamid that the regulations were useless. This Court has in the past issued opinion after opinion stating the importance of enforcing the regulations applicable at the time of operative events which flow from the regulations. There is no legal precedent in the safety regulatory system for the approach the Ohio Southern District court and the circuit court used to determine the standard of conduct which would control rights of recipients of drugs and/or vaccines and questions of the public health.

American Cyanamid argued successfully below that its non-compliance with the regulations was excused by the amendment to the five tissue culture safety rule in 1991 (one of the bases for the Grahams' claim) -- and thereafter, as the Sixth Circuit Court of Appeals found at the behest of American Cyanamid -- the obsolete regulations were all abolished in 1996. 350 F.3d at 514. This retroactive application of regulatory amendments to an operative event giving rise to a cause of action runs counter to the jurisprudence of this Court and of this country.

Justice Scalia has stated that the presumption against retroactive legislation is deeply rooted in our jurisprudence and embodies a legal doctrine centuries older than our Republic. Elementary considerations of fairness dictate that individuals should have an opportunity to know what the law is and to conform their conduct accordingly; settled expectations should not be lightly disrupted. For that reason, the "principle that the legal effect of conduct should ordinarily be assessed under the law that existed when the conduct took place has timeless and universal appeal." Kaiser Aluminum & Chemical Corp. v. Bonjorno, 494 U.S. 827, 842-844, 855-856, (1990) (Scalia, J., concurring). In a free dynamic society, creativity in both commercial and artistic endeavors is fostered by a rule of law that gives people confidence about the legal consequences of their actions. See, also, General Motors Corp. v. Romein, 503 U.S. 181, 191, (1992) ("Retroactive legislation presents problems of unfairness that are more serious than those posed by prospective legislation, because it can deprive citizens of legitimate expectations and upset settled transactions"); Munzer, A Theory of Retroactive Legislation, 61 Texas L.Rev. 425, 471 (1982) ("The rule of law . . . is a defeasible entitlement of persons to have their behavior governed by rules publicly fixed in advance");

L. Fuller, The Morality of Law, 51-62 (Yale U. Press 1977).

Even if it were the case that the regulations were no longer in effect, we respectfully submit that does not change the obligation of the vaccine manufacturer *at the time of the occurrences in question.* However, the regulations **were not amended and were not made obsolete**; as to Orimune, they were the rule of law which every physician and every parent relied on to insure that their children were not exposed to an unlicensed or unsafe product.

This Court should grant the writ so as to put to rest whether safety regulations can be made "obsolete" *nearly two decades after the individuals exposed to the product governed by those regulations have suffered paralysis which the regulations were intended to prevent.* This Court's grant of certiorari will put an end to Cyanamid's fiction that the OPV regulations *were* rendered obsolete. They were not: all that occurred was a structural *streamlining* of the existing regulations under which *all vaccines* (one of which was the oral polio vaccine) no longer needed to be regulated through *individually promulgated* regulations, because the word "standards" in the definitions of the Food and Drug Act was **expanded to incorporate the original licensing process**:

> (n) The word standards means specifications and procedures applicable to an establishment or to the manufacture or release of products, which are prescribed in this subchapter or designed to *insure the continued safety, purity and potency* of such products.

21 C.F.R. § 600.3(n) (2000) (emphasis supplied).

The regulators saw the wisdom of this Court's reliance on the licensing requirements in Berkovitz and once again emphasized as *central to the process* the same points which the Sixth Circuit ignored. The regulators understood that the tests necessary to secure a license were the best barometer by which to judge the product.

If this Court fails to grant certiorari and allows the Sixth Circuit's opinion to stand, every future litigant will be misled to believe that licensing serves no safety purpose, that the regulations' requirements of submission of safety testing data is optional for licensing a vaccine, and that even if the data are non-conforming to the standards (now, the license), it does not matter. Such an outcome is in direct conflict with the Congressional mandate, this Court's opinions, and now, even the regulator's own determination to make licensure the barometer by which to measure safety.

CONCLUSION

For all the reasons stated herein, the Petition for Writ of Certiorari should be granted.

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United States Court of Appeals,
Sixth Circuit.
Joseph R. GRAHAM, et al., Plaintiffs-Appellants,
v.
AMERICAN CYANAMID COMPANY, Defendant-Appellee.
Roy Lee Lundy, et al., Plaintiffs-Appellants,
v.
American Cyanamid Company, Defendant-Appellee.
Nos. 01-4175, 01-4176.
Argued: Aug. 1, 2003.
Decided and Filed: Dec. 3, 2003.

Reported at 350 F.3d 496

Before: DAUGHTREY, MOORE, and SUTTON, Circuit Judges.

OPINION

SUTTON, Circuit Judge.

Joseph Graham and Roy Lee Lundy, along with several members of their families, challenge the district court's order granting summary judgment to American Cyanamid Company on a series of fraud and product liability claims. American Cyanamid manufactures Orimune, which is an oral polio vaccine. Plaintiffs allege that the use of Orimune in one instance and the exposure to it in another caused a family member to contract polio.

Seeking compensation for these injuries, both sets of plaintiffs filed fraud claims against American Cyanamid, asserting that the company publicly represented Orimune as licensed, manufactured, tested and released in accordance with FDA regulations, when in fact the Orimune vaccines at issue (according to plaintiffs) did *499 not comply with FDA standards. The Graham plaintiffs separately brought strict liability and negligent failure-to- warn claims against American Cyanamid. Both sets of plaintiffs also filed derivative claims for loss of consortium and punitive damages. The district court granted American Cyanamid's motion for summary judgment on all claims. We AFFIRM.

I. BACKGROUND

A. Polio and the Orimune Vaccine.

Poliomyelitis (or polio) is a disease of the central nervous system that causes illness, paralysis and in some instances death. It affected thousands of individuals in this country during the first half of the twentieth century. *See* Dorothy M. Horstmann, *Poliovirus (Poliomyelitis), in* 2 *Textbook of Pediatric Infectious Diseases* 1186, 1189-90 (Ralph D. Feigin & James D. Cherry, eds., 1981). At its height between 1951 and 1955, polio led to 21,000 cases of paralysis per year in the United States. *See id.*

That this scourge did not continue through the second half of the twentieth century is a credit to the work of several scientists. In 1955, Dr. Jonas Salk developed the first widely successful vaccine against polio. Derived from a dead polio virus, the Salk vaccine is known as an inactivated polio vaccine ("IPV") and was licensed for production and use in the United States in 1955. *See In re Sabin Oral Polio Vaccine Prods. Liab.*

Litig., 743 F.Supp. 410, 412 (D.Md.1990) ("*Sabin I*"). The vaccine decreased the incidence of polio but did not eradicate it. Between 1958 and 1961, for example, nearly 19,000 cases of the disease were still reported in the United States. *Id.* Thirteen thousand people became paralyzed by the disease, and more than 1,000 people died from it during this period. *Id.*

At the same time that Dr. Salk was developing his vaccine, Dr. Albert Sabin began working on an oral polio vaccine ("OPV") made from attenuated strains of the polio virus. The Sabin OPV, unlike the Salk IPV, is produced from a live polio virus that has been weakened but not killed. " 'Like all vaccines cultivated from live viruses,' " such as those used for smallpox and yellow fever, " 'OPV creates immunity by inducing a mild infection in the recipient.' " *United States v. St. Louis Univ.*, 336 F.3d 294, 295 (4th Cir.2003) (quoting *Stuart v. Am. Cyanamid Co.*, 158 F.3d 622, 625 (2d Cir.1998)).

OPV has several advantages over IPV. OPV is less expensive and requires only a single dosage, while IPV requires three inoculations and a follow-up booster shot. OPV is administered orally, commonly on a sugar cube, while IPV must be injected by a hypodermic needle. The interaction of the live virus in OPV with the immune system confers lifetime immunity, while IPV requires periodic re-administration. *See generally Sabin I*, 743 F.Supp. at 412. And OPV creates "herd immunity," because an individual who has not received the vaccine can obtain immunity by contact with someone who has been vaccinated. *Id.* Individuals who have been immunized with IPV, by contrast, may still serve as carriers of the wild polio virus and may pass it on to others even though they themselves have been immunized. *Id.*

OPV, however, also has several inherent risks in view of the way it--and all vaccines developed from live viruses--work. The live but weakened viruses of OPV grow in the intestinal tract of the vaccinated individual. They eventually trigger the production of antibodies, which in turn make the individual immune to the disease after thirty days. On rare occasions, however, the virus reproduced in the vaccinee's intestinal tract reverts to the virulent *500 form. When this occurs, vaccinated individuals or persons coming in close contact with them during the thirty-day period may contract polio. Unvaccinated adults may take two precautions to avoid the risk of contracting polio: (1) alternative vaccination with IPV prior to contact with the vaccinee; or (2) avoidance of contact with the vaccinee for one month, during which time live polio viruses are being shed from the intestinal tract of the vaccinee.

In 1958 and 1959, epidemiologists conducted a series of field trials on the use of OPV. *See Sabin I,* 743 F.Supp. at 412-13. On the basis of these tests, the Surgeon General in 1960 determined that OPV was suitable for use in the United States, and it soon became the most widely used of the polio vaccines. *Id.*

The Federal Government granted licenses to three manufacturers to make live polio vaccines from the strains developed by Dr. Sabin. American Cyanamid purchased strain material that Sabin had developed, and its Lederle Laboratories division received one of the three authorized licenses from the Division of Biologic Standards ("DBS") of the National Institutes of Health to manufacture and sell OPV.

The polio virus has three types--types I, II and III--and different vaccines address each of them. Some vaccines address just one type of polio, and one vaccine

is designed to prevent all three types of polio. American Cyanamid first produced "monovalent" vaccines, which contain just one of the three types of polio virus vaccine. In 1963, however, the Federal Government granted American Cyanamid a license to make and distribute a "trivalent" vaccine, which contains all three types of polio virus vaccine. Since then, American Cyanamid has distributed a trivalent OPV product under the name Orimune.

The production of Orimune proceeds in several stages. Manufacturers initially obtain wild polio virus and attenuate its neurovirulent properties by passing it through animal hosts. What results is a "strain," which in small portions is then injected into monkey kidney cell cultures. This process, known as a "tissue culture passage," leads to the growth of more virus and the creation of vaccine "seeds." Small portions of this seed material are frozen periodically and again injected into monkey kidney cell cultures to create "pools" of vaccine for each of the three types of polio manufactured. Each monopool contains a single type of vaccine and is given a designation indicating the type of vaccine and the number of the pool (*e.g.*, 3-442 is a type III vaccine from monopool 442). Monopools for each of the vaccine types are then blended together to make a trivalent bulk "lot" that is used to fill vials. The trivalent bulk lot is given a seven-digit number and letter, such as 2054-532A. The prefix (2054) designates Orimune dosage, and the suffix (532) represents the sequential number for the trivalent bulk of that dose. The final letter (A) designates the particular filling of the final product from its trivalent bulk lot. After packaging, the manufacturer gives each lot of final containers a six-digit control number, then ships the lots to physicians, pharmacies, hospitals and clinics for use. The product is not sold directly to patients.

In the late 1970s, American Cyanamid explored

the possibility of obtaining a new type III seed to replace the seed it had been using to make most of the type III component of Orimune since the mid-1960s. At the time, another manufacturer, Pfizer, Ltd., had taken one of the "Sabin Original" strains and cloned it to create a seed known as "Sabin Original Rederived." In 1981, American Cyanamid obtained some of the Sabin Original Rederived type III seed and started using it in Orimune production.

*501 Since 1977, American Cyanamid has been the sole supplier of OPV in the United States. The annual number of cases of polio in this country has steadily declined since the widespread use of OPV. By the 1980s, fewer than twenty-five vaccine-associated cases of paralytic polio in the United States were being reported yearly, a number that dropped to an average of ten per year in the 1990s. The ten-per-year figure represents one case for every 2.6 million doses of vaccine distributed. *Sabin I,* 743 F.Supp. at 412 n. 3.

B. Federal Regulation of Polio Vaccine Production and Testing in the United States.

In view of the health and safety risks of polio vaccines, the Federal Government regulates the manufacture and distribution of them in a variety of ways. In 1961, the DBS adopted regulations governing the issuance of manufacturing licenses and the approval and release of OPV. *See* 21 C.F.R. §§ 630.10-.18 (1974) (formerly codified at 42 C.F.R. §§ 73.110-.118 (Supp.1964)). To obtain a license authorizing manufacture from the Secretary of the Department of Health, Education and Welfare under these regulations, drug manufacturers must prove that their product conforms to regulations covering all phases of the manufacturing process--beginning with the original Sabin strains of vaccine (the only strains approved in the

United States) and ending with the doses administered to patients. *See generally* 42 U.S.C. §§ 262.

Under these regulations, tests must be performed on the vaccine during various stages of production as a condition not only for licensing but also for the release of each monopool and the filling of the product. *See* Federal Food, Drug and Cosmetic Act, 21 U.S.C. §§§§ 301 *et seq.;* 21 C.F.R. §§§§ 200 *et seq.* (1977); Public Health Act, 42 U.S.C. §§ 262. Certain regulations are addressed solely to manufacturers of OPV. *See* 21 C.F.R. §§§§ 630.10-17; *Berkovitz ex rel. Berkovitz v. United States,* 486 U.S. 531, 541, 108 S.Ct. 1954, 100 L.Ed.2d 531 (1988). Others are addressed specifically to the Federal Government. *See, e.g.,* 21 C.F.R. §§§§ 600.3 *et seq.,* 630.17(e). To distribute any dose of Orimune, American Cyanamid thus had to obtain a license from the government and allow the government to test each batch of vaccine before releasing it for use.

The regulations in effect in the 1970s required that vaccine monopools be tested in monkeys for neurovirulence before they could be used for production of vaccine. *See* 21 C.F.R. §§ 630.16(b)(i)-(iii). "Neurovirulence is the capacity of an infectious agent to produce pathologic effects on the central nervous system." *Berkovitz,* 486 U.S. at 543 n. 9, 108 S.Ct. 1954. In performing tests for neurovirulence, samples of each monopool are injected at different dilutions into the brain stems of thirty monkeys and into the spinal cords of at least fifteen other monkeys. After these injections, the monkeys are sacrificed and their spinal and brain tissues are microscopically examined by qualified pathologists who conduct a "comparative evaluation" of the monopool being tested relative to identical tests performed on samples of a "Reference Attenuated Poliovirus" provided by the FDA. *See* 21 C.F.R. §§

630.16(b)(iii). The evaluation examines:

(a) the number of animals showing lesions characteristic of poliovirus infection, (b) the number of animals showing lesions other than those characteristic of poliovirus infection, (c) the severity of the lesions, (d) the degree of dissemination of the lesions, and (e) the rate of occurrence of paralysis not attributable to the mechanical injury resulting from inoculation trauma. *502 *Id.* A given monopool passes the neurovirulence test "if a comparative analysis of the test results demonstrates that the neurovirulence of the test virus pool does not exceed that of the Reference Attenuated Poliovirus." *Id.*

Among the FDA regulations governing these neurovirulence tests at this time were a "consistency of manufacture" regulation and a "tissue culture passage" regulation. The "consistency of manufacture" regulation required that no lot of vaccine be released "unless each monovalent pool contained therein is one of a series of five consecutive pools of the same type, each having been manufactured by the same procedures, and each having met the criteria of neurovirulence for monkeys prescribed in §§ 630.16(b)(1)...." *Id.* §§ 630.17(b). The "tissue culture passage" regulation required that all polio "[v]irus in the final vaccine shall represent no more than five tissue culture passages from the original strain...." *Id.* §§ 630.13(a).

Over time, the FDA modified its regulations governing the manufacture, testing and release of OPV, prompting disagreements over how the regulations should be interpreted. Some of these disagreements resulted in lawsuits under the Federal Tort Claims Act ("FTCA") between the Federal Government and individuals allegedly injured by the vaccine. In 1981, the

FDA's Bureau of Biologics assured American Cyanamid that the vaccine produced from the Pfizer seed, though rederived from the Sabin Original, did not violate the "tissue culture passage" regulation. However, several FTCA plaintiffs argued generally that the Federal Government had failed to interpret its regulations correctly and as a result had released an excessively neurovirulent Orimune vaccine, which violated the "tissue culture passage" regulation. *See Sabin I,* 743 F.Supp. at 410; *In re Sabin Oral Polio Vaccine Prods. Liab. Litig.,* 763 F.Supp. 811 (D.Md.1991), *aff'd,* 984 F.2d 124 (4th Cir.1993) ("*Sabin II*"); *Griffin v. United States,* 500 F.2d 1059 (3d Cir.1974). Similar claims were brought against vaccine manufacturers. *See Jones v. Am. Cyanamid Co.,* 139 F.3d 890, 1998 WL 116171 (4th Cir. Mar.17, 1998); *Am. Cyanamid Co. v. St. Louis Univ.,* 336 F.3d 307 (4th Cir.2003).

In 1991, a federal district court judge in Maryland ruled that vaccine from seed 45B165 was, in fact, more than five tissue culture passages beyond the Sabin original strain and that the FDA had violated 21 C.F.R. §§ 630.13(a) by approving that seed for use. *See Sabin II,* 763 F.Supp. at 813. The same district court, however, expressly found that Orimune made from this seed was both safe and effective:

> [M]y finding that regulatory violations occurred does not imply that the public health is or has been endangered in any respect. According to the undisputed record, the OPV used in the United States has always been 'state of the art' vaccine and the OPV program has resulted in the virtual eradication of wild poliovirus in the Western Hemisphere.

Id. After characterizing the country's OPV program as "perhaps the most successful public health program in history," *id.*, the court held that the FDA's only error with respect to seed 45B165 was in not "amend[ing] ... the regulations" to allow the Pfizer seed to be the "starting point" for counting tissue culture passages--something that "would clearly be proper and in the public interest." *Id.* at 825. The Fourth Circuit affirmed this judgment. *See In re Sabin Oral Polio Vaccine Prods. Liab. Litig.*, 984 F.2d 124 (4th Cir.1993).

As a result of the *Sabin* decisions, the FDA amended its polio vaccine regulations. *See* *503 Additional Standards for Viral Vaccines; Poliovirus Vaccine Live Oral, 56 Fed.Reg. 21,418, 21,422 (May 8, 1991). It amended 21 C.F.R. §§ 630.13(a) to provide that "[v]irus in the final vaccine shall represent no more than five tissue culture passages from the original strain or no more than five tissue culture passages from a virus clone derived from one of the first five tissue culture passages of the original strain." *Id.* at 21,433. At the same time, the agency repealed and amended several other regulations, including the "consistency of manufacture" regulation. In doing so, the FDA determined that, based on extensive experience with the vaccine in the field, the repealed regulations did not impact vaccine safety. *See id.* at 21,431.

C. *Graham v. American Cyanamid Co.*

Zachary Graham was born on May 2, 1984. On July 3, 1984, his mother, Lisa Graham, took him to one of the offices of Delaware Family Practice, P.C. to receive an Orimune polio vaccine. The vaccine dose came from lot 739-472, which was derived from seed 45B165. The type III component of this lot was manufactured from monopool 3-486.

The dose of Orimune that Zachary Graham received contained the following warning from American Cyanamid:

ADVERSE REACTIONS:

> Paralytic disease following the ingesting of live poliovirus vaccines has been, on rare occasion, reported in individuals receiving the vaccine ... and in persons who were in close contact with vaccinees. The vaccine viruses are shed in the vaccinee's stools for at least 6 to 8 weeks as well as via the pharyngeal route. Most reports of paralytic disease following ingestion of the vaccine or contact with a recent vaccinee are based on epidemiological analysis and temporal association between vaccination or contact and the onset of symptoms. Most authorities believe that a causal relationship exists.
>
> The risk of vaccine-associated paralysis is extremely small for vaccinees, susceptible family members and other close personal contacts. However, prior to administration of the vaccine, the attending physician should warn or specifically direct personnel acting under his authority to convey the warnings to the vaccinee, parent, guardian, or other responsible person of the possibility of vaccine-associated paralysis. The Centers for Disease Control report that during the years 1969 through 1980 approximately 290 million doses of [ ]OPV were

distributed in the United States. In the same 12 years, 25 "vaccine-associated" and 55 "contact vaccine-associated" paralytic cases were reported. Twelve other "vaccine-associated" cases have been reported in persons (recipients and contacts) with immune deficiency conditions. These statistics do not provide a satisfactory basis for estimating these risks on a per person basis.

When the attenuated vaccine strains are to be introduced into a household with adults who have not been adequately vaccinated or whose immune status cannot be determined, the risk of vaccine-associated paralysis can be minimized by giving these adults three doses of IPV a month apart before the children receive ORIMUNE. The CDC reports that no paralytic reactions to IPV are known to have occurred since the 1955 cluster of poliomyelitis cases caused by vaccine that contained live polioviruses that had escaped inactivation.

The Immunization Practices Advisory Committee of the U.S. Public Health Service states: "Because of the overriding importance of ensuring prompt and complete immunization of the child *504 and the extreme rarity of OPV-associated disease in contacts, the Committee recommends the administration of OPV to a child regardless of the poliovirus-vaccine status of adult household contacts. This is the usual

> practice in the United States. The responsible adult should be informed of the small risk involved. An acceptable alternative, if there is strong assurance that ultimate, full immunization of the child will not be jeopardized or unduly delayed, is to immunize adults according to the schedule outlined above before giving OPV to the child."

In addition to this warning, Lisa Graham signed an "Important Information" consent form provided by the Ohio Department of Health. It stated that she understood the risks and benefits associated with OPV and had been given an opportunity to ask questions about OPV that were answered to her satisfaction. The form also stated: "[O]nce in about every 4 million vaccinations, persons who have been vaccinated or who come in close contact with those who have recently been vaccinated are permanently crippled and may die. Even though these risks are low, they should be recognized." And the form made known the availability of IPV as an alternative polio vaccine with "no known risk of causing paralysis."

On July 26, 1984, Zachary Graham began experiencing fever, irritability, lethargy and general weakness. He was admitted to Grady Memorial Hospital in Delaware, Ohio, where he remained until July 29, 1984. The Centers for Disease Control in Atlanta diagnosed Zachary with Type III poliomyelitis caused by the Orimune vaccine that he had received earlier in the month. As a result of the illness, Zachary Graham became permanently disabled in his lower extremities. The Grahams initially filed a petition in the United States Court of Federal Claims on September 27, 1990, seeking compensation under the "no fault" provisions of

the National Vaccine Injury Compensation Act, 42 U.S.C. §§§§ 300aa-10 *et seq.* (Supp. 1990). Because his paralysis occurred before the Act's effective date of October 1, 1988, however, it limited the amount of compensation Zachary could receive for his injuries to $30,000. 42 U.S.C. §§ 300aa-15(b). Graham's family thereafter filed a motion to dismiss their petition voluntarily, which the United States Court of Federal Claims granted on December 10, 1993.

On May 10, 1994, Zachary's parents, Joseph and Lisa Graham, filed this action against American Cyanamid in the Southern District of Ohio (Eastern Division) on behalf of Zachary, who was then a minor. Their complaint sought compensatory and punitive relief under a variety of state-law theories: (1) strict products liability; (2) fraud; (3) negligence; (4) breach of implied warranty of merchantability; (5) breach of implied warranty of fitness; and (6) breach of express warranty.

D. *Lundy v. American Cyanamid Co.*

On March 24, 1977, Janet Lundy took her young son, Jason, to an office of the Jackson County Combined General Health District for a routine check-up. There, Dr. Carl Greever gave Jason a dosage of Orimune for immunization from polio. On April 19, 1977, Jason's father, Roy Lee Lundy, began experiencing fever, headaches, diarrhea, myalgia, malaise and general weakness. After a brief stay at Mercy Hospital in Portsmouth, Ohio, Roy's doctors transferred him to The Ohio State University Hospital in Columbus. About a week later, he was diagnosed with type III poliomyelitis, which led to permanent paralysis.

*505 Roy's doctors advised him that the probable source of the disease was the Orimune vaccine given to

Jason, which likely had been transmitted to him through close contact with his son. Jason Lundy's vaccine came from lot 480- 277 or lot 483-269. The type III component of Orimune in lot 480-277 was manufactured from a mixture of monopools 3-427 and 3-436. The type III component in lot 483-269 was manufactured from a single monopool--3-437. The evidence does not establish which lot was responsible for the Orimune vaccine that Jason ingested.

The Lundys allege that they did not suspect that American Cyanamid had acted wrongfully until they saw a television program on vaccine-induced cases of polio on September 27, 1985. After viewing this program, the family initially attempted to recover for their injuries in state court.

1. State Court Action

On March 13, 1987, Lisa and Roy Lee Lundy filed an action in the Franklin County Court of Common Pleas against (1) Lederle Laboratories, a Division of American Cyanamid, (2) the Board of Health of the Jackson Combined General Health District and (3) Dr. Carl Greever. *See Lundy v. Lederle Laboratories, Div. of Am. Cyanamid Co.,* 54 Ohio App.3d 192, 561 N.E.2d 1027 (1988). Roy Lee Lundy sought compensatory and punitive relief under a variety of theories: (1) negligence; (2) failure to obtain informed consent from the plaintiffs; (3) failure to warn; (4) breach of implied warranties of merchantability and fitness; (5) strict liability; and (6) breach of express warranties. Janet Lundy separately filed a claim for loss of consortium.

The Franklin County Court of Common Pleas eventually granted motions to dismiss on behalf of all defendants. The Ohio Court of Appeals for the Tenth District affirmed these decisions.

In November 1990, the Lundy plaintiffs filed a petition in the United States Court of Federal Claims seeking compensation under the National Vaccine Injury Compensation Act, 42 U.S.C. §§ 300aa-10 *et seq.* On March 11, 1994, the Lundys voluntarily withdrew their petition in view of the limited size of the award authorized by the Act. *See* 42 U.S.C. §§ 300aa-15(b).

2. Federal Court Action

On May 10, 1994, Roy, Janet and Jason Lundy filed this action in federal court in the Southern District of Ohio (Eastern Division), naming American Cyanamid as the only defendant. They sought compensatory and punitive relief under the following state-law theories of liability: (1) strict products liability; (2) fraud; (3) negligence; (4) breach of implied warranty of merchantability; (5) breach of implied warranty of fitness; and (6) breach of express warranty. Janet and Jason Lundy each filed independent loss-of-consortium claims. American Cyanamid filed a motion for judgment on the pleadings, arguing that all of the claims were barred by *res judicata* (due to the prior state-court action) and the statute of limitations. With the exception of Roy's fraud claim and Jason's loss-of-parental-consortium claim, the district court dismissed each of the other claims as barred by *res judicata* on September 29, 1995.

The two remaining Lundy claims were consolidated with the Graham plaintiffs' claims. On July 15, 1998, after considerable discovery, American Cyanamid filed separate motions for summary judgment against the Lundy plaintiffs and the Graham plaintiffs.

*506 **E. The District Court's Decision**

On December 21, 2000, the district court granted American Cyanamid's motions for summary judgment against the Grahams and Lundys. As to the Lundys, the court held that they had failed to submit sufficient evidence to raise a triable issue that the alleged fraudulent representations made by American Cyanamid in the package insert regarding compliance were in fact false. It further concluded that the plaintiffs had failed to submit any admissible evidence that the alleged violations had any impact on the safety of the Orimune dose that Jason Lundy received.

As to the Grahams, the court concluded that they had abandoned their fraud claim by failing to respond to American Cyanamid's summary judgment motion on the claim. It dismissed the Grahams' strict liability claim, concluding that Orimune was unavoidably unsafe. And it dismissed the Grahams' negligent failure-to-warn claim, concluding that the Orimune warnings and "Important Information" sheet provided to Zachary Graham and his mother were adequate and reasonable as a matter of law. On the basis of these rulings, the court held that the derivative nature of Jason Lundy's consortium claim and each claim for punitive damages required these claims to be dismissed as a matter of law as well. (While the district court labeled the entry disposing of all of these claims a "final judgment," neither the record nor the docket sheet reveals what happened to the three warranty claims filed by the Graham plaintiffs in their complaint. Because the Grahams do not address these claims on appeal and because the district court purported to dismiss all claims, we do not address them here.) The district court denied the Graham and Lundy plaintiffs' motions for reconsideration, and these consolidated appeals followed.

II. DISCUSSION

The customary rules for reviewing a summary-judgment decision apply. We give *de novo* review to the district court's decision. *Sperle v. Mich. Dep't of Corr.*, 297 F.3d 483, 490 (6th Cir.2002). A decision granting summary judgment is proper where no genuine issue of material fact exists and the moving party is entitled to judgment as a matter of law. Fed.R.Civ.P. 56(c). And in considering such motions, we give all reasonable factual inferences to the nonmoving party. *Matsushita Elec. Indus. Co. v. Zenith Radio Corp.*, 475 U.S. 574, 587, 106 S.Ct. 1348, 89 L.Ed.2d 538 (1986).

Our jurisdiction over these state-law claims rests on the diversity of citizenship of the parties. All of the Graham and Lundy plaintiffs are residents of Ohio. American Cyanamid, incorporated in Maine, maintains its principal place of business in New Jersey. *See* 28 U.S.C. §§ 1332. In this setting, we sit in effect as another court of the forum state, in this case Ohio, and therefore must apply its choice-of-law rules. *See Muncie Power Prods., Inc. v. United Tech Auto., Inc.*, 328 F.3d 870, 873 (6th Cir.2003). In this instance, the parties agree that those choice-of-law rules indicate that Ohio substantive law governs this claim.

All three of the tort claims in this case represent a variation on a common theme. Whether labeled fraud, strict liability, or negligent failure to warn, all three claims turn on the theory that there is a proximate connection between the alleged violations of the FDA's neurovirulence rules and the safety of the Orimune vaccine. Because we conclude that plaintiffs have failed to establish a triable issue of fact on this central point and because we conclude that each of these tort claims otherwise fails as a matter of law, we agree with the *507 District Court that the claims must be summarily

dismissed.

A. FRAUD

We begin by addressing the one claim common to both sets of plaintiffs. The Grahams and Lundys each allege that American Cyanamid acted fraudulently by representing that Orimune was licensed, manufactured, tested and released in accordance with FDA regulations when in fact it did not comply with FDA standards. To establish a cognizable claim of fraud under Ohio law, a claimant must prove the following six elements: "(a) a representation or, where there is a duty to disclose, a concealment of fact, (b) which is material to the transaction at hand, (c) made falsely, with knowledge of its falsity, or with such utter disregard and recklessness as to whether it is true or false that knowledge may be inferred, (d) with the intent of misleading another into relying upon it, (e) justifiable reliance upon the representation or concealment, and (f) an injury proximately caused by the reliance." *Russ v. TRW, Inc.*, 59 Ohio St.3d 42, 570 N.E.2d 1076, 1083 (1991). The elements of the claim are conjunctive, and accordingly all of them must be shown. *See Schwartz v. Capital Sav. & Loan Co.*, 56 Ohio App.2d 83, 381 N.E.2d 957, 959 (1978).

Both in the district court and here, the parties have vigorously contested many of these elements. Did the company in fact violate certain FDA regulations in manufacturing Orimune--specifically, the "tissue culture passage" and "consistency of manufacture" regulations? Were American Cyanamid's regulatory representations inaccurate? Did plaintiffs justifiably rely upon any of these representations? Were the representations material to product safety? And, even if all of plaintiffs' allegations are true, did the alleged regulatory violations

proximately cause these injuries? Because we conclude that the plaintiffs have failed as a matter of law to present admissible evidence of proximate cause, we address this issue and this issue (with one minor exception) alone.

Under Ohio law, plaintiffs bear the burden of establishing that American Cyanamid's alleged misrepresentation of Orimune's regulatory compliance proximately caused their injuries. *See Burr v. Bd. of County Comm'rs,* 23 Ohio St.3d 69, 491 N.E.2d 1101, 1105 (1986); *Cohen v. Lamko, Inc.,* 10 Ohio St.3d 167, 462 N.E.2d 407, 409 (1984). *See also Picklesimer v. Baltimore & O.R. Co.,* 151 Ohio St. 1, 84 N.E.2d 214 (1949) (noting that ordinary element of proximate cause applies where plaintiff has alleged fraud); Restatement (Second) of Torts §§ 557A cmt. a (noting that ordinary rules of legal cause govern fraudulent misrepresentation cases involving physical harm). To show proximate cause, the Grahams and Lundys must demonstrate that the fact allegedly misrepresented--compliance with the FDA regulations--caused their harm. *See Gaines v. Preterm-Cleveland, Inc.,* 33 Ohio St.3d 54, 514 N.E.2d 709, 712 (1987) (holding that misstatement by doctor could have caused plaintiff's physical injuries in action for fraud). That is to say, was the plaintiffs' contraction of polio a "natural and probable" (*i.e.* reasonably foreseeable) consequence of the alleged noncompliance with the regulations? *See Strother v. Hutchinson,* 67 Ohio St.2d 282, 423 N.E.2d 467, 471 (Ohio 1981); *Pfirsch v. Hall-Omar Baking Co.,* 6 Ohio App.2d 108, 216 N.E.2d 626, 628 (1966). In view of the technical and scientifically complex nature of this inquiry, only *Daubert*-qualifying expert testimony may satisfy it. *See Daubert v. Merrell Dow Pharms.,* 509 U.S. 579, 113 S.Ct. 2786, 125 L.Ed.2d 469 (1993); *cf. Berdyck v. Shinde,* 66 Ohio St.3d 573, 613 N.E.2d 1014, 1022 (1993).

*508 The Fourth Circuit recently addressed the issue of proximate cause in a similar context in *American Cyanamid Co. v. St. Louis University,* 336 F.3d 307 (4th Cir.2003). In that case, St. Louis University sued American Cyanamid, seeking contribution for a state-court judgment arising from vaccine- related injuries suffered by one of its patients. St. Louis University claimed that the Orimune vaccine violated the FDA "tissue culture passage" and "consistency of manufacture" neurovirulence regulations. In doing so, however, the university failed to produce expert testimony establishing that a polio vaccine violating these FDA regulations was any more likely to cause injury than a fully compliant vaccine. "[I]n analyzing the element of proximate cause in claims against Cyanamid," the district court initially explained, "the focus must be on whether the plaintiff can prove that it was a defect in the OPV that resulted in his injury, not simply ... whether he had been exposed to OPV derived from a seed that had been improperly approved in violation of the regulatory process." *St. Louis Univ. v. United States,* 182 F.Supp.2d 494, 500 (D.Md.2002). Applying Missouri law, the district court held that a "violation of the OPV regulations is not sufficient to prove the element of proximate cause in a context ... where a plaintiff must prove that it is more likely than not that it was excessive neurovirulence in a dose of vaccine that caused him to contract polio." *Id.* at 501. The Fourth Circuit affirmed, holding that St. Louis University "presented no expert testimony showing that [the patient] would not have contracted polio or would have contracted a less severe case of polio had he been given a vaccine complying with the neurovirulence regulations." 336 F.3d at 310.

Today's case parallels *St. Louis University* in many

ways. It involves the same defendant, the same Orimune vaccine, the same FDA regulations, the same allegations of non-compliance and the testimony of two of the same experts--Drs. Almond and Steinman. A different state's law applies, to be sure--here Ohio law, there Missouri law. *St. Louis University* of course comes from a different Circuit. And some differences in the evidence and apparently in the nature of the tort claims exist as well. But in the end we see the issue in much the same way *St. Louis University* did. Under Ohio law, as under Missouri law, plaintiffs must show that American Cyanamid's alleged misrepresentation of Orimune's regulatory compliance proximately caused their injuries. Because the Grahams and Lundys have not made out a tenable claim of proximate cause in this respect (and more specifically because they have not produced expert testimony that supports this claim), their claims must be dismissed as a matter of law.

As in *St. Louis University,* Drs. Almond and Steinman did not satisfy the proximate cause requirement in either a general or a specific manner. They did not show as a general matter that American Cyanamid's alleged regulatory noncompliance increased the risk that the Orimune vaccine would cause polio in recipients or those in close contact with recipients, beyond the inherent risk long known to be associated with OPV. Plaintiffs' statistician, Dr. Krieger, attempted to perform a statistical analysis to determine if one could "predict based on the [neurovirulence test] results of the lot whether somebody [i]s more likely or less likely to get polio from that particular lot, if it were released." Krieger Dep. at 18 (testifying in *Campagna v. Am. Cyanamid Co.*, 767 A.2d 996 (2001)). But he did not find a correlation or any study supporting the existence of such a correlation. *Id.*

*509 Plaintiffs and their experts do not fare any better in discussing the alleged violation of specific neurovirulence regulations. They initially claim, for example, that the vaccines at issue violate the "tissue culture passage" regulation. At the time of manufacture, this regulation required the vaccines to be no more than five tissue culture passages from the Sabin original strain, *see* 21 C.F.R. §§ 630.13(a), on the theory that more than five tissue culture passages would increase monkey neurovirulence. The Lundys cite a single article, published in 1961, to support their claim of a causal connection between monkey neurovirulence and the likelihood of vaccine- associated paralytic polio. *See* R. Murray, *Standardization, Licensing, and Availability of Live Polio Vaccine,* 175 J.A.M.A. 843 (1961). While the article states that "[n]eurovirulence for monkeys ... has some correlation with safety in man," it equivocates on the extent of that relationship, noting that "many strains exist which, while causing evidence of infection in monkeys, apparently cause no discernible disease in man." *Id.* at 845. In the end, the article fails to address whether a causal connection between monkey neurovirulence and paralytic polio exists and indeed never references tissue culture passage. No less importantly, the Lundys offer no studies, data or expert testimony establishing any such connection.

When questioned about compliance with the 1984 "tissue culture passage" regulation, it is true, Dr. Almond opined that Orimune exceeded the permissible tissue culture passage limits. At the same time, however, he called the regulation "daft" and in need of change, and did not opine that failure to comply with the regulation would lead to a more dangerous vaccine. More specifically, Dr. Almond testified as follows about the regulation:

A. [T]he move to Pfizer seed was a sensible development and a desirable development. But in light of that development and in light of the decision to do it, the maintaining of a regulation which said you couldn't be more than five passages away from [the original strain] was daft. It should have been changed.
Q. They should have amended the regulation?
A. They should have amended the regulation.
Q. Now, if they had amended the regulation--
A. Before giving it to Zachary?
Q. Yes.
A. That would have been fine.

Almond Dep., June 9, 1998, at 171-72.

Some seven months after this deposition and six months after American Cyanamid filed its motion for summary judgment, Dr. Almond executed a new affidavit to "explain" his previous references to the "daft" regulation. Almond Aff., Jan. 14, 1999, ¶¶ 7. In that affidavit, he claims that *American Cyanamid* was "daft" in not seeking to have the regulation amended before producing Orimune from the Pfizer seed. *Id.* As the district court noted, however, "a party cannot create a factual issue by filing an affidavit which contradicts earlier deposition testimony after a motion for summary judgment has been made. If an affidavit is untimely and inconsistent with prior discovery responses, it is inadmissible and should not be considered." *Graham v. Am. Cyanamid Co.*, 2000 WL 1911431, slip op. at 18 (S.D.Ohio Dec.21, 2000). *See Hughes v. Vanderbilt Univ.*, 215 F.3d 543, 549 (6th Cir.2000). No less importantly, Dr. Almond's affidavit never contradicts his deposition testimony that the FDA should have changed its regulation.

In 1991, when the FDA did amend this regulation,

it expressly recognized the absence *510 of any correlation between observed monkey neurovirulence and the risk of vaccine-associated paralytic polio.

> No single vaccine lot has been associated with an increased incidence of poliomyelitis. The lots that have been identified as associated with a case of paralytic poliomyelitis have had typically low scores when tested by FDA and the manufacturer for neurovirulence in monkeys.

56 Fed.Reg. at 21,420. With respect to the now-repealed "tissue culture passage" regulation, in short, plaintiffs have not established that this alleged regulatory noncompliance increased the risk that the Orimune vaccine would cause polio in recipients or those in close contact with recipients.

Plaintiffs also contend that the vaccines at issue, and more specifically the relevant monopools comprising Orimune's type III component of the vaccine, did not meet the "consistency of manufacture" regulation. As noted, this regulation required manufacturers (at the time of production) to demonstrate the genetic stability of the seed and the regularity of its manufacturing processes through the production of five consecutively and properly manufactured monovalent pools. *See* 21 C.F.R. §§ 630.17(b) ("each monovalent pool ... [must be] one of a series of five consecutive pools of the same type, each pool having been manufactured by the same procedures, and each having met the criteria of neurovirulence for monkeys....").
Again, however, plaintiffs have not produced evidence showing that a monopool that failed to satisfy the 1984 "consistency of manufacture" regulation would be more

likely to cause vaccine-associated polio than one that satisfied the requirement. When asked whether there was a scientific basis for concluding that the "consistency of manufacture" requirement was linked with product safety, Dr. Almond testified that "there is a scientific argument that you can make which would support such a conclusion ... I am not saying that is the right conclusion." Almond Dep., April 20, 1998, at 144-45. Almond added that he was not aware of any study supporting this theory. *Id.* This testimony does not suffice to create a material dispute of fact. An admissible expert's opinion, it is clear, "must be supported by more than subjective belief and unsupported speculation...." *McLean v. 988011 Ontario Ltd.*, 224 F.3d 797, 800-01 (6th Cir.2000) (quotations and citations omitted).

Nor did Dr. Steinman fill this gap. He testified that he was "not aware of any data one way or the other" showing that a violation of this regulation poses a higher risk of causing vaccine-associated paralytic polio than one satisfying the requirement. He testified:

MR. DONOVAN: Q: You understand and acknowledge that live oral polio vaccine poses a risk of vaccine-associated polio?
MR. KOPS: Objection.
THE WITNESS: Yes.
MR. DONOVAN: Q: Whether it complies with the regulations in your view or it does not comply?
THE WITNESS: A: Absolutely, yes.

Steinman Dep., June 23, 1998, at 113. The FDA's view of the former "consistency of manufacture" regulation echoes this view. In 1991, it amended and expanded the regulation in an attempt to make it more applicable to product safety.

> The former consistency requirements were based on the premise that the failure of a monovalent virus pool to meet neurovirulence requirements could be the result of a manufacturing deficiency.... [N]o criteria were provided to link the history of performance of monovalent *511 virus pools with the continued qualification of the seed virus. Long experience has shown that the failure of a monovalent virus pool, produced from an acceptable seed virus, is usually unrelated to deficiencies in the manufacturing process, but is usually due instead to test variability.... The revised methodology is at least as stringent as the former consistency requirements in detecting neurovirulence problems related to manufacturing defects, while having the added benefit of providing a statistical means for monitoring the continued qualification of a seed virus by evaluating its ability to consistently produce monovalent pools of acceptable neurovirulence.... [T]hese requirements provide assurances of consistency ... while actually reducing the likelihood that a seed virus will be rejected on the basis of test variability unrelated to genetic stability.

56 Fed.Reg. at 21,430-31. On this record, plaintiffs have not shown a connection between this regulation and product safety.

Attempting to fill this evidentiary gap, the Grahams and Lundys make a series of arguments to the effect that the alleged violations of these regulations

establish negligence *per se* and to the apparent effect that proximate cause on this fraud claim accordingly need not be shown. But the invocation of this tort doctrine by itself, whether in the context of a negligence claim or a fraud claim, does not excuse the claimant from showing that the regulation at issue has a tenable and provable connection to public safety. *See, e.g., Merchants Mutual Ins. Co. v. Baker,* 15 Ohio St.3d 316, 473 N.E.2d 827, 828 (1984) ("Negligence *per se* does not equal liability *per se.* Simply because the law may presume negligence from a person's violation of a statute or rule does not mean that the law presumes that such negligence was the proximate cause of the harm inflicted."); *see also Chambers v. St. Mary's School,* 82 Ohio St.3d 563, 697 N.E.2d 198, 201 (1998) (noting that negligence *per se* requires a showing of proximate cause). In this instance, the alleged violations relate to regulations that no longer are in existence, that the FDA believes did not affect public safety and that plaintiffs' experts have not been able to show affected public safety. Plaintiffs offer no example of a court (in Ohio or elsewhere) that has concluded that the invocation of "negligence *per se* " may fill this evidentiary gap. We doubt such a case exists, and at all events reject this argument as a matter of law.

Plaintiffs do not gain any more traction by turning to the 1991 *Sabin* case and other cases arising from challenges to the 1984 neurovirulence regulations. These decisions did not involve the liability of private manufacturers for regulatory violations, but rather concerned the actions of the FDA in interpreting and applying its regulations. *Sabin* itself, moreover, concludes that the regulatory violations did not affect product safety: "[T]he scientists who established and implemented the OPV program ... consistently acted in the public interest as they reasonably perceived it to be.

They made judgments on extremely difficult questions which, strictly from the standpoint of public health, appear to be entirely proper.... [M]y finding that regulatory violations occurred does not imply that the public health is or has been endangered in any respect." *Sabin II,* 763 F.Supp. at 813. What is more, Judge Motz, who presided over *Sabin II,* presided over the recent case between St. Louis University and American Cyanamid. *See St. Louis Univ.,* 182 F.Supp.2d at 494. There, Judge Motz concluded that the plaintiff's failure to prove, via expert testimony, that a regulatory violation increased the risk of paralysis meant that it could not prove any such violation by American *512 Cyanamid proximately caused the vaccinee's paralysis. *See id.* at 500-03. A similar flaw exists here.

The Lundys further allege that expired and rejected materials were included in Jason's vaccine. American Cyanamid's experts confirmed that when a trivalent product's potency is not sufficient to reach the FDA criteria for potency, it must be re-bulked. That is to say, the manufacturer combines vaccine that may not qualify for use by itself in order to reach FDA-regulated potency levels and must do so without violating another FDA regulation. The Lundy (and Graham) experts again did not offer a tenable basis for concluding that re-bulking vaccine potency with expired or rejected material negatively affects product safety.

In the end, as in *St. Louis University,* plaintiffs have not met their burden of proximately linking their allegations of regulatory non-compliance with these undisputed and indisputably-severe injuries. That evidentiary gap is particularly significant in this medical setting. All vaccines produced from live viruses, as this one is, carry the paradoxical risk of inducing the very disease that the vaccine strives to prevent. In the

absence of expert testimony showing that these alleged regulatory violations made Orimune more unsafe than it otherwise would have been, a rational trier of fact could rule for plaintiffs only on the basis of conjecture, not a legitimate set of inferences drawn from admissible evidence. On this record, it remains unknowable whether plaintiffs' injuries stemmed from an avoidable defect in the product or unavoidable bad luck. That the 1984 regulations upon which these claims rest have since been repealed and that the FDA has concluded that compliance with these regulations did not decrease the incidence of vaccine- associated paralytic polio cement this conclusion.

Unable to establish a connection between these regulations and product safety, plaintiffs also necessarily come up short in showing that the representations at issue were material. For if plaintiffs cannot show that the alleged misrepresentations affected product safety, they cannot show that they were material. All things considered, the fraud claims in both cases must be summarily dismissed.

B. STRICT LIABILITY

The Grahams separately claim that they have presented a triable issue of fact on their strict-liability claim. For many of the same reasons that their fraud claim fails, however, this claim fails as well. (The Lundys, recall, brought strict-liability and failure-to-warn claims in state court and lost; when they filed the same claims here, the district court rejected them on *res judicata* grounds; those decisions have not been appealed.)

Ohio has adopted §§ 402A of the Restatement (Second) of Torts (1965) as the standard for strict

liability. *See Temple v. Wean United, Inc.*, 50 Ohio St.2d 317, 364 N.E.2d 267, 271 (1977). It says:

> (1) One who sells any product in a defective condition unreasonably dangerous to the user or consumer or to his property is subject to liability for physical harm thereby caused to the ultimate user or consumer, or to his property, if
>
> (a) the seller is engaged in the business of selling such a product, and
>
> (b) it is expected to and does reach the user or consumer without substantial change in the condition in which it is sold.
>
> (2) The rule stated in Subsection (1) applies although
>
> (a) the seller has exercised all possible care in the preparation and sale of his product, and
>
> *513 (b) the user or consumer has not bought the product from or entered into any contractual relation with the seller.

Restatement (Second) of Torts §§ 402A. To establish strict liability under Ohio law, plaintiffs must produce expert testimony that the defect at issue "proximately caused the[ir] claimed injuries." *State Farm Fire & Cas. Co. v. Chrysler Corp.*, 37 Ohio St.3d 1, 523 N.E.2d 489, 494 (1988). *See* Ohio Rev.Code Ann. §§ 2307.73(A)(2).

Against this legal backdrop, the Grahams argue that American Cyanamid is strictly liable for Zachary's

injuries. Specifically, they claim that Orimune was defective because it violated several FDA regulations: (1) the "tissue culture test"; (2) the "consistency of manufacture test"; and (3) the FDA's licensing requirements. They further argue that the warning accompanying the Orimune dose Zachary received was inadequate.

The Grahams' strict-liability claim fails for the same reason that their fraud claim fails and for the same reason that the Fourth Circuit recently rejected identical claims in *American Cyanamid Co. v. St. Louis University*, 336 F.3d at 307. They have not been able to show that the alleged regulatory violations--non-compliance with the "tissue passage culture" and "consistency of manufacture" regulations--proximately caused Zachary Graham's illness. Just as the expert testimony relied upon by the Grahams and Lundys did not show proximate cause in support of their fraud claims, the same expert testimony fails to do so here. In the absence of admissible evidence of proximate cause, the Grahams' product defect claim under the 1984 "tissue culture passage" and "consistency of manufacture" regulations fails as a matter of law.

The Grahams also claim that the Orimune vaccine Zachary received was defective because American Cyanamid was not properly licensed to manufacture it. While they question whether certain testing procedures necessary for licensing occurred, they offer no evidence that the company did not in fact have a valid license to manufacture Orimune. As with their other claims, they also offer no evidence that any anomalies in American Cyanamid's license proximately caused Zachary's injuries. In Ohio, the absence of a valid or properly issued license does not by itself establish the proximate cause of an injury. *Cf. Gulla v. Straus*, 154 Ohio St. 193,

93 N.E.2d 662, 664 (1950).

Plaintiffs also argue that the defense under Ohio law for "unavoidably unsafe" drugs is not available to American Cyanamid because the company allegedly violated FDA regulations. *See White v. Wyeth Labs.*, 40 Ohio St.3d 390, 533 N.E.2d 748, 752 (1988) ("a manufacturer of an unavoidably unsafe product may not be held strictly liable for injuries caused thereby, provided that the product was '... properly prepared, and accompanied by proper directions and warning ...' ") (quotation omitted); Restatement (Second) of Torts §§ 402A, cmt. k (recognizing that certain products exist that cannot be made completely safe for their intended use and, when properly prepared, and accompanied by proper directions and warnings, are not defective, nor unreasonably dangerous). The availability of this defense, however, does not come into play in this instance, because plaintiffs have failed to establish their affirmative case by showing a causal relationship between the asserted defect--alleged regulatory violations--and Zachary's injury. *See St. Louis Univ.*, 336 F.3d at 311 n. 4.

C. NEGLIGENT FAILURE TO WARN

The Grahams independently bring a negligent failure-to-warn claim. *See* *514 *Crislip v. TCH Liquidating Co.*, 52 Ohio St.3d 251, 556 N.E.2d 1177, 1181-82 (1990). The claim has three elements, each of which must be satisfied: (1) a duty to warn against reasonably foreseeable risks; (2) breach of this duty; and (3) an injury that is proximately caused by the breach. *See Briney v. Sears, Roebuck & Co.*, 782 F.2d 585, 587 (6th Cir.1986). Under Ohio law, the manufacturer of a prescription drug discharges its duty to warn about risks regarding prescription drugs if the manufacturer

adequately warns the patient's doctor of those risks. *See* Ohio Rev.Code Ann. §§ 2307.76(C). When a plaintiff alleges that the warning given to a prescribing physician is inadequate, the plaintiff must prove his claim through expert medical testimony. *See, e.g., Jones v. Roche Labs.*, 84 Ohio App.3d 135, 616 N.E.2d 545, 547 (1992).

As with the Grahams' other claims, this one too founders on the shoal of proximate cause. Even if we grant that the warning American Cyanamid offered was in some way inadequate, which appears not to be the case, *see supra* (reprinting warnings); *see also Kearl v. Lederle Labs.*, 172 Cal.App.3d 812, 818-19, 834-36, 218 Cal.Rptr. 453 (holding that an "Important Information" statement identical to the one Lisa Graham signed adequately informed the plaintiff of the reasonably foreseeable risks associated with OPV as a matter of law), the Grahams have not shown that this inadequacy proximately caused Zachary's injuries. *See Seley v. G.D. Searle & Co.*, 67 Ohio St.2d 192, 423 N.E.2d 831, 838 (1981). To the extent plaintiffs complain that the warning failed to acknowledge the alleged regulatory violations, they again have not shown that regulatory non-compliance in this instance had a bearing on product safety.

To the extent plaintiffs mean to complain that the warning should have noted that IPV is the preferred polio vaccine, the record contradicts that claim. The scientific community agreed long ago that "IPV and OPV are both effective in preventing poliomyelitis, [but] OPV is the vaccine of choice for primary immunization of children in the United States when the benefits and risks for the entire population are considered." *Recommendation of the Advisory Committee on Immunization Practices* 2 (1982). This was largely because of "its ease of administration (oral instead of injected),

expected long lasting immunity, and the production of bowel immunity." E.O. Nightingale, *Recommendations for a National Policy on Poliomyelitis Vaccination*, 287 N.E. J. Med. 249-53 (1977). *See also Report of Committee on Infectious Diseases* 208, 209 (1982); Institute of Medicine, *An Evaluation of Poliomyelitis Vaccine Policy Options* 28 (1988). Mass vaccination with IPV also has had little impact on polio outbreaks. In contrast, wide use of OPV brought an end to any cases of paralytic polio caused by naturally circulating polio virus in the United States in 1979 and in the Western Hemisphere in 1991. Centers for Disease Control, *Poliomyelitis Prevention in the United States: Updated Recommendations of the Advisory Committee on Immunization Practices (ACIP)*, Morbidity & Mortality Weekly Report, May 19, 2000, at 1, 5. In 1996, the FDA recognized the wide use of OPV as so successful that it officially revoked OPV regulations on the express ground that they were now "obsolete or no longer necessary to achieve public health goals." Revocation of Certain Regulations, Biological Products, 61 Fed.Reg. 40,153, 40,153 (Aug. 1, 1996).

D. DERIVATIVE CLAIMS

Jason Lundy's claim for loss of parental consortium and the Grahams' and Lundys' claims for punitive damages are derivative *515 in nature. A derivative cause of action may not provide greater relief than that available under the primary cause of action. *See Lynn v. Allied Corp.*, 41 Ohio App.3d 392, 536 N.E.2d 25, 36 (1987). Having dismissed plaintiffs' respective causes of action for fraud, strict liability, and negligent failure-to-warn as a matter of law, we must dismiss these derivative claims as well.

III. CONCLUSION

For the foregoing reasons, we AFFIRM.

UNITED STATES COURT OF APPEALS
FOR THE SIXTH CIRCUIT

Nos. 01-4175; 014176

FILED
DEC - 3 2003
LEONARD GREEN, Clerk

No. 01-4175
JOSEPH R. GRAHAM, et al.,
Plaintiffs - Appellants,

v.

AMERICAN CYANAMID COMPANY,
Defendant - Appellee.

No. 01-4176
ROY LEE LUNDY, et al.,
Plaintiffs - Appellants,

v.

AMERICAN CYANAMID COMPANY,
Defendant - Appellee.

Before: DAUGHTREY, MOORE, and SUTTON, Circuit Judges.

JUDGMENT

On Appeal from the United States District Court
for the Southern District of Ohio at Columbus.

THIS CAUSE was heard on the record from the district court and was argued by counsel.

IN CONSIDERATION WHEREOF, it is ORDERED that the judgment of the district court is AFFIRMED.

ENTERED BY ORDER OF THE COURT

Leonard Green

Leonard Green, Clerk

United States District Court,
S.D. Ohio, Eastern Division.

Joseph R. GRAHAM, et al., Plaintiffs,
v.
AMERICAN CYANAMID COMPANY, Defendant.

Roy Lee LUNDY, et al., Plaintiffs,
v.
AMERICAN CYANAMID COMPANY, Defendant.
Nos. C-2-94-423, C-2-94-425.

Dec. 21, 2000.

[Reported at 2000 WL 1911431]

OPINION AND ORDER

SMITH, District Judge

[*1] Plaintiffs Roy Lee Lundy and Zachary Graham assert state law claims alleging that they became permanently disabled by a polio vaccine (named "Orimune") that was manufactured by defendant American Cyanamid Co. Jason Lundy, as a child of Roy Lee Lundy, brings a derivative claim for loss of parental consortium based on product defect and failure to warn. This matter is before the Court on defendant's motion for summary judgment in each case. For the reasons herein, the Court grants defendant's motion for summary judgment in both cases. [FN1]

FN1. The Court also denies plaintiffs' motion of May 18, 1999 that seeks a stay of disposition of

defendant's summary judgment motion, a "Bratka" hearing, and an order of the U.S. Marshall to seize all of defendant's records concerning the production, manufacture, and testing of Orimune between 1972 and 1984 (Doc. 188).

I. BACKGROUND

Poliomyelitis and the Orimune Vaccine

Polio is a disease of the central nervous system. In 1955, Dr. Jonas Salk developed a vaccine against polio. Dr. Salk's vaccine was an inactivated polio vaccine ("IPV") derived from a dead polio virus. The Salk vaccine decreased the incidence of polio but did not eradicate it. While Dr. Salk was developing his IPV, which had to be injected, Dr. Albert Sabin, among others, was working on an oral polio vaccine ("OPV"). The OPV, unlike the IPV, is produced from live polio virus that is weakened, but not killed.

OPV has advantages over IPV. First, OPV is less expensive and requires only a single dose, as opposed to three inoculations of IPV and a follow-up booster shot. Second, OPV is administered orally, commonly on a sugar cube, while IPV must be injected by a hypodermic needle. Third, the interaction of the live virus in OPV with the immunological system confers lifetime immunity. IPV, in contrast, requires periodic readministration. Fourth, the oral administration stimulates the body's production of antibodies in the gastrointestinal tract as well as in the bloodstream, thereby producing bowel immunity which interrupts the method of transmitting the wild strain of the virus. Persons vaccinated with OPV shed vaccine viruses through feces and saliva to nonvaccinated persons, thereby conferring immunity on them as well.

There are, however, inherent risks with the administration of OPV. The live but weakened viruses of OPV grow in the intestinal tract of the vaccinated individual. The growing viruses trigger the vaccinee's immune system to produce antibodies which makes the vaccinee immune to the disease after thirty days. However, on extremely rare occasions, the virus reproduced in the vaccinee's intestinal tract reverts to the virulent form. When this occurs, the vaccinee or persons coming in close contact with the vaccinee during the thirty day period may contact polio. Unvaccinated adults can take two precautions to avoid the risk of "contact polio": (1) alternative vaccination with IPV prior to contact with the vaccinee; or (2) avoidance of contact with the vaccinee for one month, during which time live polio viruses are being shed from the intestinal tract of the vaccinee.

In 1960, the Surgeon General declared that OPV was suitable for use in the United States. In 1961, the Division of Biologic Standards of the National Institutes of Health ("DBS") adopted regulations governing the issuance of manufacturing licenses and the approval and release of OPV. Cyanamid purchased strain material that had been developed by Sabin and allegedly applied to DBS for a license to manufacture and sell OPV. Since 1963, Cyanamid has distributed an OPV product under the name Orimune, and since 1977, Cyanamid has been the sole supplier of OPV in the United States.

[*2] Orimune is composed of all three Sabin strains of live polio virus corresponding to the three different types of polio, known as Types I, II, and III. This results in the designation "trivalent." Because of the inherent risks in the Sabin strains, the Secretary of the Department of Health, Education, and Welfare promulgated regulations to protect susceptible persons form contacting the disease. 21 C.F.R. §§§§ 630.10-630.18 (formerly codified at 42 C.F.R. §§§§ 73.110-73.118). Drug manufacturers

had to prove its product's conformity with these regulations before the Secretary could issue a license authorizing manufacture. 42 U.S.C. §§ 262(d).
Orimune is not sold directly to patients, but rather is distributed to physicians, hospitals, and clinics.

Graham, et al., v. American Cyanamid Co

Plaintiff Zachary Graham was born on May 2, 1984. On July 3, 1984, he was taken to one of the offices of Delaware Family Practice, P.C. for an administration of Orimune for the immunization from polio. Around July 26, 1984, Zachary Graham began experiencing fever, irritability, lethargy, and general lack of interest and was admitted to Grady Memorial Hospital in Delaware, Ohio where he remained until July 29, 1984. Plaintiff was diagnosed by the Centers for Disease Control in Atlanta as suffering from Type III poliomyelitis from the Orimune administered to him on July 3, 1984. As a result, Zachary Graham is permanently disabled in his lower extremities.

Graham plaintiffs filed a petition in the United States Court of Federal Claims, seeking compensation under the National Vaccine Injury Compensation Act. Later, they filed a motion to voluntarily dismiss the petition under the National Vaccine Injury Compensation Program, which was approved on December 10, 1993. The present action was filed on May 10, 1994 by plaintiff Zachary Graham, then a minor, by and through his parents Joseph and Lisa Graham. Graham plaintiffs bring state law claims for: (1) common law fraud; (2) strict products liability; (3) negligence; and, (4) punitive damages. Defendant Cyanamid moves for summary judgment on each of Graham plaintiffs claims.

Lundy, et. al., v. American Cyanamid Co.

On March 24, 1977, plaintiff Jason Lundy was taken by his mother for a routine check-up and given a dosage of Orimune for immunization from polio by Dr. Carl Greever, M.D., in an office of the Jackson County Combined General Health District. On April 19, 1977, Jason's father, plaintiff Roy Lee Lundy, began to experience fever, headaches, diarrhea, myalgia, malaise, and great weakness. He was admitted to Mercy Hospital in Portsmouth, Ohio. He was transferred to Ohio State University Hospital in Columbus about a week later where he was diagnosed as suffering from poliomyelitis. He was advised that the probable source of the polio virus was the Orimune given to his son and that it had likely been transmitted to him through close contact with his son. Roy Lee Lundy's poliomyelitis is a permanent condition and has rendered him a paraplegic.

[*3] The package insert that accompanied the Orimune administered to Jason Lundy in March 1977 included a warning that "paralytic disease following the ingestion of live poliovirus vaccines has been reported in individuals receiving the vaccine, and in some instances, in persons who were in close contact with subjects who had been given live oral poliovirus vaccine." This warning mirrored the Orimune entry in the 1977 Physicians' Desk Reference that warned of the rare occurrence of paralytic disease "in persons who were in close contact with subjects who had been given live oral poliovirus vaccine" and that "those parents of a vaccinee who have not had previous polio vaccination should probably be considered among those adults as subject to increased risk of exposure and in this special situation, in the judgment of the physician responsible, protection may be needed for these intimate contacts." Both the package insert and the Physicians' Desk Reference entry for Orimune also contained a statement that Orimune had been licensed, manufactured, tested, and released in accordance with FDA regulations.

Plaintiffs allege that they did not suspect that defendant had acted wrongfully until they saw a television program on vaccine-induced cases of polio on September 27, 1985. After viewing this program, Lundy plaintiffs attempted to recover for their injuries by filing an action in state court and a petition in the United States Court of Federal Claims. Judge David Cain dismissed each of the Lundys' actions for bodily injury and loss of spousal consortium as time-barred. Lundy plaintiffs then filed the present action.

In this action, Lundy-plaintiffs raise six state law claims for relief: (1) strict product liability; (2) fraud; (3) negligence; (4) breach of implied warranty of merchantability; (5) breach of implied warranty of fitness for a particular purpose; (6) breach of express warranty; and (7) loss of parental consortium by Jason Lundy. Each of the Lundys' claims, except the fraud and loss of parental consortium claims, were dismissed by Judge Holschuh on September 29, 1995 having been raised and dismissed with prejudice in the previous state court action. Defendant now moves for summary judgment on Roy Lee Lundy's fraud claim and Jason Lundy's loss of parental consortium claim.

II. SUMMARY JUDGMENT STANDARD

The procedure for granting summary judgment is found in Fed.R.Civ.P. 56(c), which provides:

> The judgment sought shall be rendered forthwith if the pleadings, depositions, answers to interrogatories and admissions on file, together with the affidavits, if any, show that there is no genuine issue as to any material fact and that the moving party is entitled to judgment as a matter of law.

The evidence must be viewed in the light most favorable to the nonmoving party. *See Adickes v. Kress & Co.*, 398 U.S. 144, 158-59, 90 S.Ct. 1598, 26 L.Ed.2d 142 (1970). Summary judgment will not lie if the dispute about a material fact is genuine; "that is, if the evidence is such that a reasonable jury could return a verdict for the nonmoving party." *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 248, 106 S.Ct. 2505, 91 L.Ed.2d 202 (1986). Summary judgment is appropriate, however, if the opposing party fails to make a showing sufficient to establish the existence of an element essential to that party's case and on which that party will bear the burden of proof at trial. *See Celotex Corp. v. Catrett*, 477 U.S. 317, 322, 106 S.Ct. 2548, 91 L.Ed.2d 265 (1986); *see also Matsushita Electric Industrial Co., Ltd. v. Zenith Radio Corp.*, 475 U.S. 574, 106 S.Ct. 1348, 89 L.Ed.2d 538 (1986).

[*4] When reviewing a summary judgment motion, the Court must view all of the evidence in the record. *See Reeves v. Sanderson Plumbing Products, Inc.*, 530 U.S. 133, 120 S.Ct. 2097, 2110, 147 L.Ed.2d 105 (2000). The Court must draw all reasonable inferences in favor of the nonmoving party, and must refrain from making credibility determinations or weighing the evidence. *Id.* Although the Court views the entire record, it disregards all evidence favorable to the moving party that the jury is not required to believe. *Id.* Stated otherwise, the Court must credit evidence favoring the nonmoving party as well as evidence favorable to the moving party that is uncontroverted or unimpeached, if it comes from disinterested witnesses. *Id.*

The Sixth Circuit Court of Appeals has recognized that *Liberty Lobby, Celotex* and *Matsushita* have effected "a decided change in summary judgment practice, ushering in a 'new era' in summary judgments." *Street v. J.C. Bradford & Co.*, 886 F.2d 1472, 1476 (6th Cir. 1989).

The court in *Street* identified a number of important principles applicable in new era summary judgment practice. For example, complex cases and cases involving state of mind issues are not necessarily inappropriate for summary judgment. *Id.* at 1479. In addition, in responding to a summary judgment motion, the nonmoving party "cannot rely on the hope that the trier of fact will disbelieve the movant's denial of a disputed fact, but must 'present affirmative evidence in order to defeat a properly supported motion for summary judgment.' " *Id.* (quoting *Liberty Lobby,* 477 U.S. at 257). The nonmoving party must adduce more than a scintilla of evidence to overcome the summary judgment motion. *Id.* It is not sufficient for the nonmoving party to merely "show that there is some metaphysical doubt as to the material facts." *Id.* (quoting *Matsushita,* 475 U.S. at 586).

III. DISCUSSION

1. Fraud

Plaintiffs assert that defendant acted fraudulently by falsely representing that Orimune was licensed, manufactured, tested, and released in accordance with FDA regulations and that defendant made unspecified false and misleading representations concerning the degree of risk associated with contracting polio as a result of ingestion or contact with someone who had ingested Orimune. [FN2] Plaintiffs also claim defendant acted fraudulently by failing to disclose that Orimune had not complied with FDA regulations. Plaintiffs allege that defendant's misrepresentations and omissions "were made to induce medical care providers to continue to use Orimune ... and to induce reliance by medical care providers on those representations in the care and treatment of persons receiving Orimune, including [plaintiffs]" (Complaint, ¶¶ 32).

FN2. The Court will address plaintiffs contention that the defendant made unspecified false and misleading statement in regard to the risk inherent in the ingestion of Orimune in the Court's analysis of plaintiff's failure to warn claim infra.

Under Ohio law, the elements of fraud are: (1) a representation, or concealment where there is a duty of disclosure; (2) which is material to the issue at hand; (3) that is made falsely, with knowledge of its falsity, or with such reckless or utter disregard as to its truth or falsity that knowledge may be inferred; (4) with the intent of misleading another into relying upon such representation or concealment; (5) where one at whom the representation or concealment was directed justifiably, or reasonably, relied upon the representation or concealment; and, (6) an injury proximately caused by the reliance resulted. *See Burr v. Bd. of Cty. Comm'rs of Stark County,* 23 Ohio St.3d 69, 491 N.E.2d 1101 (1986). It is eminently clear under Ohio law that plaintiffs must prove fraud by a preponderance of the evidence in an action at law. *See Household Finance Corp. v. Altenberg,* 5 Ohio St.2d 190, 214 N.E.2d 667 (1966); *Weiss v. Kearns,* 11 Ohio St.2d 73, 228 N.E.2d 331 (1967). [FN3]

FN3. Counsel for defendant has set forth in its filings that the proper standard for fraud in this case where a legal remedy is sought is clear and convincing evidence (94-425, Doc. 163, pp. 2, 7; 94-423, Doc. 166, pp. 16-18). This is incorrect. It is basic and widely-regarded Ohio law that a fraud action that seeks an equitable remedy (i.e. declaratory judgment, reformation or recission of

a contract) must be proved by clear and convincing evidence, while a fraud action that seeks a monetary remedy must be proved by the lower preponderance standard. The cases that defendant's counsel has chosen to cite for its incorrect proposition of law are peculiar (94-425, Doc. 163, p. 7, §§ 1; 94-423, Doc. 166, p. 17, n. 7). The first case, *Zehe v. Caugherty*, 1989 WL 7948, is an unpublished appellate decision of the 8 th District. Surely, in researching the law, counsel would have begun with the Supreme Court of Ohio and found *Household Finance* and other cases citing this proposition. Even if counsel had mistakenly searched cases of the Cuyahoga Court of Appeals first, they would have discovered upon due diligence the more recent case of *Watkins v. Cleveland Clinic Found.*, 130 Ohio App.3d 162, rendered only two years ago, that cites correctly the *Household Finance* proposition. It appears that defendant's counsel dug until they were able to find an opinion with a standard sufficiently vague that it could be used to attempt to deceive this Court into using an incorrect legal standard. The second case, *Kern v. Kern*, 100 Ohio App. 327, 136 N.E.2d 675 (1955), is an appellate decision of the 9 th District wherein the plaintiff is seeking a declaratory judgment to quiet title in real property in himself-- an equitable remedy. The third case cited by defendant's counsel, *In re Lamberton's Estate*, 142 Ohio St. 417, 52 N.E.2d 855 (1944), is an action by estate beneficiaries to set aside the payment of an allegedly fraudulent judgment by the estate's administrator out of the proceeds of the estate-- also an equitable action. While citing these three cases, defendant's counsel ignored or failed to discover the endless string of cases citing the law

of *Household Finance* and its progeny. The Court does not have patience with counsel that acts to willfully mislead it on matters of law. The Court notes, in fact, that this violates the Ohio, Pennsylvania, and New York Codes of Professional Responsibility. The Court will assume in this matter that defendant's counsel has acted negligently rather than willfully to mislead the Court. However, the Court urges counsel in the future to perform due diligence and be truthful in its filings with the Court.

[*5] It appears that Graham plaintiffs have abandoned their fraud claim. As defendant points out in its Reply Memorandum (94-423, Doc. 183, p. 19), and as best this Court can ascertain, Graham plaintiffs have failed to respond to or present any evidence to defeat defendant's summary judgment motion on this issue as required under Fed. R. Civ. Proc. 56©© and subsequent cases (See 94- 423, Doc. 180) . [FN4] Defendant's summary judgment motion as to the Graham's fraud claim is therefore granted.

FN4. Graham plaintiffs title Doc. 180 "Plaintiffs' Memorandum in Opposition to ... Motion For Summary Judgment on the Grahams' ... Fraud ... Claim." Graham plaintiffs also state on page one that American Cyanamid engaged in "egregious fraud on the American medical community and the public." Graham plaintiffs' next mention of fraud is on page33, where they write, "[t]here is no privilege for fraud." Graham plaintiffs discuss warnings alleged falsity on page 60. Yet, there is no presentation of evidence of fraud or discussion of its elements.

For a plaintiff to succeed on a claim of fraud, he must demonstrate that the representation was false, or that the plaintiff concealed a material issue of fact. Defendant argues that the assertion made in the representations accompanying the dosage of Orimune administered to Jason Lundy were in compliance with FDA regulations and therefore not false. [FN5] *See* 42 CFR 73.114 *et seq.* [FN6] The parties agree that the vaccine administered to Jason Lundy originated from either control numbers 483-269 or 480-277. The type III component of Orimune in 483-269 was manufactured from monopool 3-437. Plaintiffs' expert, Dr. Jeffrey Almond, agreed that monopool 3-437 satisfied FDA regulations as they existed at that time (Almond Depo., p. 106-08). It is also undisputed that the FDA authorized the release of 3-437 on October 22, 1975 (94-423, Doc. 165, Exh. 3, Exh. C, p. 3).

FN5. Specifically, the statement included in the vaccine package insert administered to Jason Lundy read:

DISCLAIMER OF REPRESENTATIONS AND WARRANTIES

This vaccine has been produced and tested in accordance with regulations of the United States Food and Drug Administration for the production of polio virus vaccine, live, oral. The manufacturer makes no representation of warranty, expressed or implied, with respect to the merchantability of fitness for use of this vaccine other than that the vaccine has been produced in accordance with the standards for its production prescribed by the United States Food and Drug Administration and applicable thereto at the time of its release by the manufacturer. While the use of this preparation and other measures described herein are

consistent with accepted standards of medical practice, their use as described cannot be expected necessarily to assure a specific result.

Doc. 163, Exh. 3A.

FN6. These regulations are cited as they were originally promulgated and as they were in effect when plaintiffs in these cases contracted poliomyelitis. Since that time, they have been recodified in 21 CFR §§§§ 630.10-630.17. On August 1, 1996, the Food and Drug Administration removed 21 CFR 630, summarizing that the regulations were "obsolete or no longer necessary to achieve public health goals." *See* Federal Register, August 1, 1996, Vol. 61, No. 149, p. 40155.

The type III component of Orimune in 480-277 was manufactured from a combination of monopools 3-427 and 3-436. Dr. Almond testified that monopool 3-436 satisfied then-existing FDA regulations (Almond Depo., p. 106). It is also undisputed that the FDA authorized the release of 3-436 on July 16, 1975 (94-423, Doc. 165, Exh. 3, Exh. C, p. 2). Monopool 3-427 also was part of control number 480-277. Plaintiffs' expert, Dr. Lawrence Steinman, testified that the intraspinal and intrathalamic tests performed on monkey hosts did not demonstrate a "severity" score that was different than the reference test scores as performed by the FDA (Steinman Depo., pp. 83-93; Doc. 163, Exh. 14). Given this information, Dr. Steinman testified that the FDA's decision to release monopool 3-427 warranted deference (Steinman Depo., pp. 93-97). This evidence creates an inference that the type III Orimune in control numbers 480- 277 and 483-269 was licensed and manufactured in accordance with FDA regulations, and therefore, defendant's representation of compliance with

FDA regulations on the accompanying insert was in fact true.

The plaintiffs argue at great length that defendant was not duly licensed *ab initio* to manufacture any oral polio vaccine by the FDA, and therefore, the specific vaccine administered to Jason Lundy, though approved for release itself, should not have been released based on a lack of enumerated requirements. It contends that defendant did not complete each step required in order to obtain its original license, including submitting a sample of the vaccine product, measuring the safety of the product at every stage of the manufacturing process, and submitting a license and results of each test performed and a sample of the finished product. *See* 42 U.S.C. §§ 262(a); 42 C.F.R. §§ 73 (1964); 21 C.F.R. §§ 601 (1987); *Berkowitz v. United States,* 486 U.S. 531, 540-541, 108 S.Ct. 1954, 100 L.Ed.2d 531 (1988). Thus, plaintiffs contend that defendant's authority to produce oral polio vaccine never existed. As proof of this, plaintiffs submit that neither defendant nor the government can produce the application authorizing defendant to product oral polio vaccine (94-425; Doc. 207, p. 13). Plaintiffs argue this conclusively evidences a failure to satisfy the licensing requirements. Yet, the mere absence of records does not indicate that a license was never granted. Administrative agencies are afforded a presumption of regularity in regard to adherence to their own regulations. *See Bowen v. Amer. Hosp. Assoc.,* 476 U.S. 610, 626-27, 106 S.Ct. 2101, 90 L.Ed.2d 584 (1986); *Motor Vehicles Ass'n of U.S. v. State Farm Mut. Auto. Ins. Co.,* 463 U.S. 29, 42-43, 103 S.Ct. 2856, 77 L.Ed.2d 443 (1983), f. 9; *Schweiker v. McClure,* 456 U.S. 188, 195, 102 S.Ct. 1665, 72 L.Ed.2d 1 (1982); *Bd. of Trustees of Ohio St. Univ. v. U.S. Dept. of Educ.,* 849 F.2d 1472,*8 (6 th Cir.1988)(unpublished opinion). For plaintiffs to demonstrate that defendant acted wholly without authority, they must present some affirmative

evidence that the National Institute of Health did not grant a license to defendant. [FN7] For example, plaintiffs could discover or seek release of DBS records of all applications received or all licenses issued and demonstrate that there is an absence of an application or grant of license to defendant. Fed.R.Evid. 803(6), (7), (10). Their argument fails as a matter of law because they have failed to present this affirmative evidence.

> FN7. In 1972, the Department of Biologic Standards was transferred from the National Institute for Health to the Food and Drug Administration and renamed the Bureau of Biologics. *See* 37 Fed.Reg. 12865 (1972).

[*6] Assuming that the plaintiffs allegations that defendant was not properly licensed to manufacture OPV is accurate, the evidence does not demonstrate that this lack of regulations proximately caused plaintiffs injuries. *See Burr*, 23 Ohio St.3d at 73, 491 N.E.2d 1101. Rather, the evidence indicates that there are risks inherent in the ingestion of OPV regardless of whether the manufacturer was licensed. Dr. Steinman testified as follows:

MR. DONOVAN: Q: You understand and acknowledge that live oral polio vaccine poses a risk of vaccine-associated polio?
MR. KOPS: Objection.
THE WITNESS: Yes.
MR. DONOVAN: Q: Whether it complies with the regulations in your view or it does not comply?
THE WITNESS: A: Absolutely, yes.
(Steinman Depo., p. 113). In sum, the Court finds that plaintiffs have failed to adduce affirmative evidence showing misrepresentation in the form of a lack of

license to manufacture polio vaccine.

Reliance is also a necessary element of plaintiff's fraud claim. *See Burr,* 23 Ohio St.3d at 73, 491 N.E.2d 1101. Plaintiff Roy Lundy argues that his reliance should be presumed (Doc. 207, p. 32). Plaintiff cites *Rubin v. Schottenstein, Zox, & Dunn,* 143 F.3d 2632 (6 th Cir.1998) as support for this proposition. Yet, as plaintiff correctly notes, *Rubin* concerns the presumption of reliance for fraud in connection with the purchase or sale of securities under federal Rule 10b-5 and its "fraud on the market" theory. Conversely, the case at bar concerns a claim of fraud under Ohio common law. The Sixth Circuit and other circuits have held that the presumptions necessarily given to investors because of the nature of securities and security markets and the necessary protection of investors, does not apply in common law fraud. *See In re Sofamor Danek Group, Inc.,* 123 F.3d 394, 403-04 (6 th Cir.1997); *Mergens v. Dreyfoos,* 163 F.3d 1114, 1118, 1999 WL 46751,*4 (11 th Cir.1996), *Basham v. Gen. Shale Products Corp.,* 989 F.2d 491, 1993 WL 65086,*4, fn. 4 (4 th Cir.1993). The evidence indicates that Roy Lee Lundy was not present when his son was vaccinated (Roy Lee Lundy Depo., p. 103). The evidence also demonstrates that Roy Lee Lundy did not speak with anyone, including medical professionals, about the benefits and risks of oral polio versus inactivated polio vaccine (Roy Lee Lundy Depo., pp. 111-112). Roy Lee Lundy also testified that he was not aware of an alternative inactivated polio vaccine at that time and did not know whether his son was offered the alternative killed vaccine (Roy Lee Lundy Depo., p. 112). Plaintiff has therefore not proven reliance as is necessary to support a claim for common law fraud. For this additional reason, Roy Lee Lundy's fraud claim is accordingly dismissed.

2. Product Defect

Graham plaintiffs claim that defendant is strictly liable for defective manufacture of the Orimune dosage provided to Zachary Graham. A federal court sitting in diversity must follow the law directed by the Supreme Court of the state whose law is applicable, and if there is no direct decision by the highest court of that state, the federal court should determine what it believes that state's highest court would find if the issue were before it. *See Meredith v. Winter Haven,* 320 U.S. 228, 234-37, 64 S.Ct. 7, 88 L.Ed. 9 (1943). The parties agree that Ohio law is applicable in this case.

[*7] Ohio has adopted Section 402A of Restatement of the Law 2d, Torts (1965) with respect to strict products liability. *See Temple v.. Wean United, Inc.,* 50 Ohio St.2d 317, 4 O.O.3d 466, 364 N.E.2d 267 (1977). Section 402A provides:

> "(1) One who sells any product in a defective condition unreasonably dangerous to the user or consumer or to is property his subject to liability for physical harm thereby caused to the ultimate user or consumer, or to his property, if
>
> > "(a) the seller is engaged in the business of selling such a product, and
> >
> > "(b) it is expected to and does reach the user or consumer without substantial change in the condition in which it is sold.
>
> "(2) The rule stated in subsection (1) applies although
>
> > "(a) the seller has exercised all possible care in the preparation and sale of his product, and
> >
> > "(b) the user or consumer has not bought the product from or entered into any contractual relation with the seller."

Ohio later adopted Comment k to Section 402A which provides an exception to the strict liability of manufacturers for injuries and damages caused by defective products which are "unavoidably unsafe." *See Seley v. G.D. Searle & Co.*, 67 Ohio St.3d 192, 21 O.O.3d 121, 423 N.E.2d 831 (1981). Comment k recognizes that there are products that exist that are incapable of being made safe for their ordinary and intended use. Yet, their production, marketing, and use are justified because they provide great societal benefits that outweigh their inherent risk.

The seller of a drug is not strictly liable for injury resulting from use of an unavoidably unsafe product only if the product has been prepared properly and adequate warning of all potential adverse reactions inherent in the use of the drug are included with the product. *See* Restatement of Torts 2d, Section 402A, Comment k; *Seley*, 67 Ohio St. at 197. Therefore, when the product is manufactured improperly or when the drug manufacturer fails to give adequate warning, the drug may be considered "defective" and unreasonably dangerous, thereby subjecting the manufacturer to strict liability for resulting injury. [FN8] *See id.*

> FN8. Courts have had difficulty in distinguishing negligence and strict liability claims where the defect alleged is based on a Section 402A inadequate warning. Strict liability focuses, not on the conduct of the manufacturer, but rather on the condition of the product. Yet, the manufacturer's provision of adequate warning has been said to sound in negligence. This, however, overlooks Section 402A, where the duty is one of

strict liability where care is irrelevant. The ultimate issue is whether the product was unreasonably dangerous, thus defective, because the warning was inadequate, rather than how it became inadequate.

Plaintiffs argue that the polio vaccine administered to Zachary Graham was unreasonably dangerous because: (1) it was defectively manufactured under the "tissue culture passages" test; (2) it was defectively manufactured based upon the "consistency of manufacture" test; and, (3) it was defectively manufactured because defendant was not licensed at the time it manufactured plaintiff's polio vaccine.

Plaintiffs assert that Graham's vaccine was defectively manufactured because it violated a regulation that required the type III component of the vaccine to be no more than five "tissue culture passages" from the original strain. 21 C.F.R. §§ 630.13(a). Plaintiffs, however, have offered only conclusory arguments as to this assertion and have not presented evidence in its Response Memorandum in Opposition to avoid summary judgment under Rule 56. Specifically, plaintiffs state that "American Cyanamid was at the sixth tissue culture passage as to Type III, and the sixth, seventh, or who knows what passage as to Type I and Type II. Therefore, American Cyanamid had no knowledge about this product." (Doc. 180, p. 40). These conclusory contentions, in the absence of affirmative evidence, are not sufficient to demonstrate a triable issue of fact. As such, plaintiffs argument is not well-taken.

[*8] Plaintiffs also argue that the vaccine administered to Zachary Graham was defective because it was not one of five consecutive monopools that passed the monkey neurovirulence test. The vaccine administered to Zachary Graham emanated from control number 3-486,

which was descendant from seed 45B165. In order to satisfy the monkey neurovirulence test as it then existed, 3-486 must have been one in a series of at least five lots that passed the monkey neurovirulence test. Plaintiffs experts, Drs. Almond and Steinman, both testified that 3-486 was one of a series of at least five lots that satisfied this test under the regulations as they then existed. Dr. Almond testified:

Q: Turning your attention to that same page we were looking at a moment ago, which is bar code 23914.
MR. KOPS: That's NA2 tests?
Mr. YOERGES: No, 23914 is the 45B165 tests.
THE WITNESS: 488.
BY MR. YOERGES:
Q: Look at the test results for 486 through 490. Just tell me that based on these results--and I know we did some of this before--do the monopools satisfy or not satisfy the regulations in your opinion?
MR. KOPS: Objections.
THE WITNESS: They satisfy.
(Almond Depo., p. 155).
Dr. Steinman testified similarly:
Q: Okay. Looking at Exhibit 7 on I think the last page, the first of those monopools is 3-486; right?
A: Right.
Q: 3-486, based on the results in this exhibit, satisfies the requirement both on the IS [intraspinal] and IT [intrathalamic]; is that correct?
A: 3-486, yes.
Q: And 3-487 passes both the IS and IT; correct?
A: Yes.
Q: And 488 passes both IS and IT?
A: Yes.
Q: And 489 passes both?
A: Yes.
Q: And 490 passes both?
A: Right.

. . .
Q: 3-486 both passes the requirements as one of five consecutive passing lots based on Exhibit 7; correct?
MR. KOPS: Objection.
A: Yes.
(Steinman Depo., p. 115-116).

As can best be drawn from plaintiffs' briefs, plaintiff has presented no evidence other than Dr. Almonds' affidavit executed six months after his deposition testimony on the eve of the filing of plaintiffs' Memorandum in Opposition that seeks to modify or alter his deposition testimony (Doc. 180, Exh. 20.). A party cannot create a factual issue by filing an affidavit which contradicts earlier deposition testimony after a motion for summary judgment has been made. If an affidavit is untimely and inconsistent with prior discovery responses, it is inadmissable and should not be considered. *See Hughes v. Vanderbilt Univ.*, 215 F.3d 543, 549 (6 th Cir.2000); *Russell v. Ohio River Co.*, 960 F.2d 149, 1992 WL 78104,*3 (6 th Cir.1992)(unpublished opinion).

Plaintiffs also argue that the vaccine administered to Zachary Graham was defective because defendant was not licensed to manufacture polio vaccine when Zachary Graham's vaccine was produced. Plaintiff, however, has presented no evidence to substantiate this allegation (Doc. 180, p. 40). The Court has already addressed this argument, *supra*, and found it to be without merit.

[*9] The warning accompanying the vaccine must also have been adequate under Comment k for the product to be unavoidably unsafe. The question of the adequacy of the warning given in strict liability cases has been deemed to be perhaps the central issue in determining whether the product is unreasonably dangerous within the concept of strict liability as set forth in Section 402A. *See Seley* at 197. Where an adequate warning is

provided, the action must be determined in favor of the manufacturer irrespective of whether the plaintiff's use of the drug was, in fact, causally connected to the plaintiff's injury, and despite the fact that the product is unavoidably unsafe. *See id.*

In order to be adequate, the warning must reasonably disclose to the medical profession all risks inherent in the use of the drug which the manufacturer knew or should have known to exist, being held to the standard of an expert in that field. *See Seley,* at 197, 198. A warning may be unreasonable in its factual content, its expression of the facts, or the method or form in which it is conveyed. *See id.* at 198, 423 N.E.2d 831. The adequacy of warnings is measured not only by what is stated, but also by the manner in which it is stated. A reasonable warning not only conveys a fair indication of the nature of the dangers involved, but also warns with the degree of intensity demanded by the nature of the risk. A warning may be inadequate if it is unduly delayed, reluctant in tone, or lacks a sense of urgency. *See id.*

The plaintiffs argue that the warning provided to the medical professional who administered Orimune to Zachary Graham was inadequate. [FN9] The warning provided:

> FN9. Under Ohio law, the duty to warn depends upon the drug manufacturer's relationship to the user. Where a prescription drug has been prescribed for a patient by the patient's physician, the manufacturer has been held to discharge its duty to warn if the manufacturer adequately warns the physician. *See Tracy v. Merrell Dow Pharamaceuticals, Inc.,* 58 Ohio St.3d 147, 149, 569 N.E.2d 875 (1991). This duty to warn is termed the

learned intermediary rule. Ohio adopted the learned intermediary rule in *Seley*. If the product is properly labeled with the apprropriate warnings and instructions to fully inform the physician of the risks involved and the procedures for use, the manufacturer may reasonably assume that the physician will exercise informed judgment in the patients best interest. *See Tracy,* at 150, 569 N.E.2d 875.

ADVERSE REACTION:

Paralytic disease following the ingestion of live poliovirus vaccines has been, on rare occasion, reported in individuals receiving the vaccine, (see for example CONTRAINDICATIONS) and in persons who were in close contact with vaccines. The vaccine viruses are shed in the vaccinee's stools for at least 6 to 8 weeks as well as via the pharyngeal route. Most reports of paralytic disease following ingestion of the vaccine or contact with a recent vaccinee are based on epidemiological analysis and temporal association between vaccination or contact and the onset of symptoms. Most authorities believe that a causal relationship exists.

The risk of vaccine-associated paralysis is extremely small for vaccinees, susceptible family members and other close personal contacts. However, prior to administration of the vaccine, the attending physician should warn or

specifically direct personnel acting under his authority to convey the warnings to the vaccinee, parent, guardian, or other responsible person of the possibility of vaccine-associated paralysis. The Centers for Disease Control report that during the years 1969 through 1980 approximately 290 million doses of TOPV were distributed in the United States. In the same 12 years, 25 "vaccine-associated" cases and 55 "contact vaccine-associated" paralytic cases were reported. Twelve other "vaccine-associated" cases have been reported in persons (recipients or contacts) with Immune deficiency conditions. These statistics do not provide a satisfactory basis for estimating these risks on a per person basis.

[*10] When the attenuated vaccine strains are to be introduced into a household with adults who have not been adequately vaccine or whose immune status cannot be determined, the risk of vaccine-associated paralysis can be minimized by giving these adults three doses of IPV a month apart before the children receive ORIMUNE. The CDC reports that no paralytic reactions to IPV are known to have occurred since the 1955 cluster of poliomyelitis cases caused by vaccine that contained live poliovirus that has escaped inactivation.

The Immunization Practices Advisory Committee of the U.S. Public Health Service states: "Because of the overriding importance of ensuring prompt and complete immunization of the child

> and the extreme rarity of OPV-associated disease in contacts, the Committee recommends the administration of OPV to a child regardless of poliovirus-vaccine status of adult household contacts. This is the usual practice in the United States. The responsible adult should be informed of the small risk involved. An acceptable alternative, if there is strong assurance that ultimate, full immunization of the child will not be jeopardized or unduly delayed, is to immunize adults according to the schedule outlined above before giving OPV to the child."]

In addition to the warning received from the defendant, Lisa Graham, as parent for Zachary Graham, signed a consent form presented to her by the Ohio Department of Health stating that she understood the risks and benefits associated with oral polio vaccine and had had the opportunity to ask questions which were answered to her satisfaction (Doc. 164, Exh. 4). This form stated that:

> "Once in about every 4 million vaccinations, person who have been vaccinated or come in close contact with those who have recently been vaccinated are permanently crippled and may die. Even though these risks are low, they should be recognized."

The form also noted the availability of an injectable, or killed, polio vaccine which "has no known risk of causing paralysis." Plaintiff Lisa Graham testified that she did not read the consent form throughly, that she only "glanced through it," and that she "didn't read it word for word" (Doc. 164, Exh. 5). Plaintiffs now seek to claim that they were not aware of the warnings or that the

warnings were inadequate. The Court finds that the warnings presented to Graham plaintiffs were adequate as a matter of law. The Court finds that the oral polio vaccine could not have been designed at the time of its distribution to Zachary Graham so as to effectively accomplish the same purpose of immunization of the widespread public with any less risk. Accordingly, the Court finds that the oral polio vaccine Orimune administered to plaintiff Graham was unavoidably unsafe as a matter of law. Plaintiffs' strict liability claim is therefore dismissed.

3. Failure to Warn

Graham plaintiffs also assert a claim for negligent failure to warn. [FN10] The manufacturer of a product owes a duty to exercise reasonable care in the design, manufacture, and marketing of the product so as to avoid injuring foreseeable users and third persons. *See Temple v. Wean United, Inc.*, 50 Ohio St.2d 317, 364 N.E.2d 267, (1977). A claim for negligent failure to warn has three basic elements: (1) a duty to warn against reasonably foreseeable risks; (2) breach of such a duty; and, (3) injury that is proximately caused by the breach. *See Briney v. Sears, Roebuck & Co.*, 782 F.2d 585, 587 (6 th Cir.1986)(citing *Menifee v. Ohio Welding Products, Inc.*, 15 Ohio St.3d 75, 77, 472 N.E.2d 707(1984)). [FN11]

FN10. Under Ohio law, plaintiffs may assert both a claim for negligent failure to warn, and failure to warn under a theory of strict liability, where a failure to warn renders a product unreasonably dangerous. *See Crislip v. TCH Liquidating Co.*, 52 Ohio St.3d 251, 256, 556 N.E.2d 1177 (1990). Even though it is not

particularly evident from the plaintiffs filings if they have raised both causes of action, the Court will presume that it has done so. *See id.* at 258, 556 N.E.2d 1177. Since this Court has discussed failure to warn in strict liability in the previous section, this section will discuss plaintiffs' claims for negligent failure to warn.

FN11. The analysis of strict liability and negligent failure to warn overlap, yet are distinct theories of recovery. Both theories concern the adequacy of warnings provided by the manufacturer. An inaccurate warning, however, may give rise to separate and distinct causes of action under either theory of recovery. In strict products liability, the focus is on the condition of the product. Thus, the warning is part of the design of the product and the product itself is considered unreasonably dangerous if the warning is inaccurate. Where warnings are necessary to a safe design, a manufacturer is charged with hindsight as to the potential risk of injury. In negligent failure to warn, however, the focus is instead on the conduct of the manufacturer. Under the negligence theory of recovery, a manufacturer must warn the consumer of latent defects inherent in the use of the product, including those form foreseeable misuse. In this case, the manufacturer is not charged with hindsight, but only with reasonable care under the circumstances. *See Tipton v. Michelin Tire Co.*, 101 F.3d 1145, 1149-1150 (6th Cir. 1996).

[*11] The manufacturer must give suitable warning of a dangerous propensity that may result in use of the product. *See Temple,* 50 Ohio St.2d at 272-73, 364 N.E.2d 27 (1977). The defendant's duty in this case is to use ordinary care in acting as the reasonably prudent manufacturer of oral polio vaccine in the same or similar circumstances. The warning necessary to satisfy the duty of ordinary care will, of course, vary depending on the facts of each case. *See Miles v. Kohli & Kaliher Assoc., Ltd.,* 917 F.2d 235, 243 (6 th Cir.1990). In this case, use of defendant's OPV could foreseeably result in serious injury. As a result, reasonableness requires defendant to warn any user of potential risks using appropriate explanatory and cautionary language. Having determined that the defendant owed a duty to warn the plaintiffs, the Court now turns to determining whether the competent evidence viewed in a light most favorable to plaintiffs support the argument that this duty has been breached.

In the use of certain drug and vaccines, simple instructions may be inadequate to convey the gravity of the risk. Though the Supreme Court of Ohio has not recognized the concept of unreasonably dangerous and unavoidably unsafe products outside of the context of strict liability under §§ 402A, the Sixth Circuit has found these concepts instructive in analyzing negligent failure to warn. *See Miles,* 917 F.2d 235, 245-46 (6 th Cir.1990), fn. 9. A warning may be inadequate, and therefore unreasonable, in its factual content, its expression of the facts, or the method or form in which it is conveyed. *See Seley,* at 198. The record indicates a warning was included in the package of vaccine administered to Zachary Graham. This warning was quoted in its entirety in part two *supra.*

The evidence also indicates, as discussed above, that Lisa Graham signed a separate consent form

presented to her by the health clinic that warned her of the risk of the live, oral polio vaccine and offered her the opportunity to immunize her son with the injected, inactivated vaccine. Plaintiff Lisa Graham testified that she did not read the consent form throughly, that she only "glanced through it," and that she "didn't read it word for word" (Doc. 164, Exh. 5).

The Graham plaintiffs also allege that defendant was negligent per se and discuss at great length the facts surrounding this allegation. The Court has stressed on several occasions, *supra,* that plaintiffs have presented no competent evidence that defendant violated any law or regulation promulgated for the governing of oral polio vaccines.

Based on the above, the Court finds that reasonable minds could come to but one conclusion that the warnings provided by defendant were adequate and, therefore, reasonable as a matter of law. The Graham plaintiffs negligent failure to warn claim is therefore dismissed.

4. Jason Lundy's Loss of Parental Consortium Claim/Grahams' and Lundys' Claims for Punitive Damages

[*12] Defendant has filed for summary judgment on plaintiff Jason Lundy's claim for loss of parental consortium based upon product defect and failure to warn and also with regard to Graham and Lundy plaintiffs claim for punitive damages. Claims for loss of consortium are derivative in nature and cannot succeed if the underlying primary claim is dismissed. The derivative cause of action cannot provide greater relief than that permitted for the primary cause of action. *See Bacon v. Kirk,* 2000 WL 1648925,*22 (2000); *Lynn v. Allied Corp.,* 41 Ohio App.3d 392, 402, 536 N.E.2d 25, 36 (1987); *Messmore v. Monarch Machine Tool Co.,* 11 Ohio App.3d 67, 463 N.E.2d 108 (1983). Likewise, a

claim for punitive damages is derivative. *See Moshkovitz v. Mt. Sinai Med. Ctr.*, 69 Ohio St.3d 638, 650, 635 N.E.2d 331 (1994). The Ohio Supreme Court has held that "no civil cause of action may be maintained simply for punitive damages." *Bishop v. Grdina*, 20 Ohio St.3d 26, 28, 485 N.E.2d 704 (1985). Punitive damages cannot therefore be granted unless plaintiff succeeds in proving actual, compensatory damages. *See Malone v. Courtyard by Marriott Ltd. Partnership*, 74 Ohio St.3d 440, 447, 659 N.E.2d 1242 (1996); *Bennett v. Stanley*, 1999 WL 1254814,*14 (1999), fn. 6. The Court also notes that it does not appear that Graham plaintiffs have presented any evidence in opposition to defendant's motion for summary judgment on their punitive damages claim as required under Fed. R. Civ. Proc. 56 (Doc. 180). Inasmuch as this Court has discussed these claims, *supra*, as they relate to the defendant, and having found that the evidence warrants a grant of summary on each claim, the Court forthwith dismisses these derivative claims as well.

IV. CONCLUSION

Based on the foregoing, the Court GRANTS defendant's summary judgment motions. The Clerk shall enter final judgment in these actions in favor of defendant, and against plaintiffs, dismissing these actions in their entirety with prejudice.

The Clerk shall remove these cases and their attendant pending motions from the Court's pending cases and motions lists.

IT IS SO ORDERED.

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF OHIO

FILED
KENNETH J. MURPHY
CLERK
00 DEC 21 AM 8:40
U.S. DISTRICT COURT
SOUTHERN DIST. OHIO
COLUMBUS

JUDGMENT IN A CIVIL CASE

Joseph R. Graham, et al

vs. Case No. C2-94-423

American Cyanamid Company Judge Smith

Magistrate Judge King

[ ] Jury Verdict. This action came before the court for a trial by jury. The issues have been tried and the jury has rendered a verdict.

[ ] Decision by Court. This action came to trial or hearing before the Court. The issues have been tried or heard and a decision has been rendered.

[X] Decision by Court. This action was decided by the Court without a trial or hearing.

IT IS ORDERED AND ADJUDGED that pursuant to the Opinion and Order of December 21, 2000, summary judgment is granted in favor of defendant American Cyanamid Company and this action is DISMISSED WITH PREJUDICE.

Date: December 21, 2000

Kenneth J. Murphy, Clerk

By: Peg Lambert

Peg Lambert, Deputy Clerk

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF OHIO

FILED
KENNETH J. MURPHY
CLERK
00 DEC 21 AM 8:40
U.S. DISTRICT COURT
SOUTHERN DIST. OHIO
COLUMBUS

JUDGMENT IN A CIVIL CASE

Roy Lee Lundy, et al

vs. Case No. C2-94-425

American Cyanamid Company Judge Smith

Magistrate Judge King

[ ] Jury Verdict. This action came before the court for a trial by jury. The issues have been tried and the jury has rendered a verdict.

[ ] Decision by Court. This action came to trial or hearing before the Court. The issues have been tried or heard and a decision has been rendered.

[X] Decision by Court. This action was decided by the Court without a trial or hearing.

IT IS ORDERED AND ADJUDGED that pursuant to the Opinion and Order of December 21, 2000, summary judgment is granted in favor of defendant American Cyanamid Company and this action is DISMISSED WITH PREJUDICE.

Date: December 21, 2000

Kenneth J. Murphy, Clerk

By: Peg Lambert

Peg Lambert, Deputy Clerk

42 U.S.C. § 262(d) (emphasis supplied):

> "Licenses for the maintenance of establishments for the propagation or manufacture and preparation of products [including polio vaccines] may be issued only upon a showing that the establishment and the products for which a license is desired meet standards, **designed to insure the continued safety, purity, and potency of such products**, prescribed in regulations, and licenses for new products may be issued only upon a showing that they meet such standards. **All such licenses shall be issued, suspended, and revoked as prescribed by regulations** . . . ."

TITLE 21--FOOD AND DRUGS

Chapter I--Food and Drug Administration, Department of Health and Human Services

Subchapter F--Biologics

Part 630--Additional Standards for Viral Vaccines

Subpart A--Poliovirus Vaccine Inactivated

* * *

§ 630.10 Poliovirus Vaccine Live Oral.

(a) Proper name and definition. The proper name of this product shall be "Poliovirus Vaccine Live Oral," followed by a designation of the type. The vaccine shall be a preparation of one or more live, attenuated polioviruses grown in monkey kidney cell cultures or a cell line found by the Director, Office of Biologics Research and Review, to meet the requirements under § 610.18(c). The vaccine shall be prepared in a form suitable for oral administration.

(b) Criteria for acceptable strains and acceptable seed virus (b)(1) Strains of attenuated poliovirus Types 1, 2, and 3 used in the manufacture of the vaccine shall be identified by: (i) Historical records including origin and techniques of attenuation, (ii) antigenic properties, (iii) neurovirulence for monkeys, (iv) pathogenicity for other animals and tissue cultures of various cell types, and (v) established virus markers including rct/40, d, and other markers shown to be associated with strain virulence.

(b)(2) Poliovirus strains shall not be used in the manufacture of Poliovirus Vaccine Live Oral, unless, (i)

data are submitted to the Director, Office of Biologics Research and Review which establish that each such strain is free of harmful effect upon administration in the recommended dosage to at least 1 million people susceptible to poliomyelitis, under circumstances where adequate epidemiological surveillance of neurological illness has been maintained, and, (ii) each such strain produces a vaccine meeting the safety and potency requirements of §§ 630.11, 630.15, and 630.16(b). Susceptibility shall be demonstrated by blood tests, stool examinations and other appropriate methods.

(b)(3) Each seed virus used in manufacture shall be demonstrated to be free of extraneous microbial agents except for unavoidable bacteriophage.

(b)(4) No seed virus shall be used for the manufacture of poliovirus vaccine unless its neurovirulence in Macaca monkeys is no greater than that of the Reference Attenuated Poliovirus distributed by the Bureau of Biologics Research and Review. The neurovirulence of the seed virus shall be demonstrated by the following tests to be performed by the manufacturer: (i) The test prescribed in § 630.16(b)(1) using seed virus as test material in place of monovalent virus pool material and (ii) the following comparative intramuscular neurovirulence test: Each of at least 10 monkeys shall be injected with a total of 5.0 ml. of the seed virus under test in one or more proximate locations of either a gluteus or gastrocnemius muscle. Similar injections shall be made in another group of 10 monkeys using the Reference Attenuated Poliovirus. Each monkey shall be injected intramuscularly with no less than 10 [FN7.7] TCID T25 T20 of viral inoculum. All monkeys shall be observed for 17 to 21 days and a comparative evaluation shall be made of the evidence of neurovirulence of the

virus under test and the Reference Attenuated Poliovirus, as prescribed in § 630.16(b)(1)(iii).

(b)(5) Subsequent and identical neurovirulence tests shall be performed in monkeys whenever there is evidence of a change in the neurovirulence of the production virus, upon introduction of a new production seed lot, and as often as necessary otherwise to establish to the satisfaction of the Director, Office Biologics Research and Review that the seed virus strains for vaccine manufacture have maintained their neurovirulence properties as set forth in § 630.16(b)(1)(iii).

(b)(6) The Director, Office of Biologics Research and Review, may, from time to time, prohibit the use of a specified strain whenever he finds it is practicable to use another strain of the same type which is potentially less pathogenic for man, and that it will produce a vaccine of greater safety and of at least equivalent potency.

§ 630.11 Clinical trials to qualify for license.

To qualify for license, the antigenicity of the vaccine shall have been determined by clinical trials of adequate statistical design conducted in compliance with Part 56 of this chapter unless exempted under § 56.104 or granted a waiver under § 56.105, and with Part 50 of this chapter. Such clinical trials shall be conducted with five lots of poliovirus vaccine which have been manufactured by the same methods. Type specific neutralizing antibody shall be induced in 80 percent or more of susceptibles when administered orally as a single dose, or in 90 percent or more of susceptibles when administered orally after a series of doses. A separate clinical trial shall have been conducted for each

monovalent and each polyvalent vaccine for which a license application is made.

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§ 630.13 Manufacture of Poliovirus Vaccine Live Oral.

(a) Virus passages Virus in the final vaccine shall represent no more than five tissue culture passages from the original strain, each of which shall have met the criteria of acceptability prescribed in § 630.10(b).

(b) Virus propagated in monkey kidney cell cultures--

(b)(1) Continuous cell lines. When primary monkey kidney cell cultures are used in the manufacture of poliovirus vaccine, continuous cell lines shall not be introduced or propagated in vaccine-manufacturing areas.

(b)(2) Identification of processed kidneys The kidneys from each monkey shall be processed and the viral fluid resulting therefrom shall be identified as a separate monovalent harvest and kept separately from other monovalent harvests until all samples for the tests prescribed in the following subparagraph relating to that pair of kidneys shall have been withdrawn from the harvest.

(b)(3) Monkey kidney tissue production vessels prior to virus inoculation Prior to inoculation with the seed virus, the tissue culture growth in vessels representing each pair of kidneys shall be examined microscopically for evidence of cell degeneration at least 3 days after complete formation of the tissue sheet. If such evidence is observed, the tissue cultures from that pair of kidneys

shall not be used for poliovirus vaccine manufacture. To test the tissue found free of cell degeneration for further evidence of freedom from demonstrable viable microbial agents, the fluid shall be removed from the cell cultures immediately prior to virus inoculation and tested in each of four culture systems: (i) Macaca monkey kidney cells, (ii) Cercopithecus monkey kidney cells, (iii) primary rabbit kidney cells, and (iv) human cells from one of the systems described in § 630.16(a)(6), in the following manner: Aliquots of fluid from each vessel shall be pooled and at least 10 ml. of the pool inoculated into each system, with ratios of inoculum to medium being 1:1 to 1:3 and with the area of surface growth of cells at least 3 square centimeters per milliliter of test inoculum. The cultures shall be observed for at least 14 days. At the end of the observation period, at least one subculture of fluid from the Cercopithecus monkey kidney cell cultures shall be made in the same tissue culture system and the subculture shall be observed for at least 14 days. If these tests indicate the presence in the tissue culture preparation of any viable microbial agent, the tissue cultures so implicated shall not be used for poliovirus vaccine manufacture.

(b)(4) Control vessels Before inoculation with seed virus, sufficient tissue culture vessels to represent at least 25 percent of the cell suspension from each pair of kidneys shall be set aside as controls. The control vessels shall be examined microscopically for cell degeneration for an additional 14 days. The cell fluids from such control vessels shall be tested, both at the time of virus harvest and at the end of the additional observation period, by the same method prescribed for testing of fluids in paragraph (b)(3) of this section. In addition, the cell sheet in each control vessel shall be examined for presence of hemadsorption viruses by the addition of guinea pig red blood cells.

(b)(5) Virus harvest; interpretation of test results If the tissue culture in less than 80 percent of the control vessels is not free of cell degeneration at the end of the observation period, no tissue from the kidneys implicated shall be used for poliovirus vaccine manufacture. If the test results of the control vessels indicate the presence of any extraneous agent at the time of virus harvest, the entire virus harvest from that tissue culture preparation shall not be used for poliovirus vaccine manufacture. If any of the tests or observations described in paragraphs (b)(3) or (4) of this section demonstrate the presence in the tissue culture preparation of any microbial agent known to be capable of producing human disease, the virus grown in such tissue culture preparation shall not be used for poliovirus vaccine manufacture.

(b)(6) Kidney tissue production vessels after virus inoculation-- temperature After virus inoculation, production vessels shall be maintained at a temperature not to exceed 35.0 degrees C. during the course of virus propagation.

(b)(7) Kidney tissue virus harvests Virus harvested from vessels containing the kidney tissue from one monkey may constitute a monovalent virus pool and be tested separately, or viral harvests from more than one pair of kidneys may be combined, identified and tested as a monovalent pool. Each pool shall be mixed thoroughly and samples withdrawn for testing as prescribed in § 630.16(a). The samples shall be withdrawn immediately after harvesting and prior to further processing, except that samples of test materials frozen immediately after harvesting and maintained at -60 degrees C. or below, may be tested upon thawing, provided no more than one freeze-thaw cycle is employed.

(b)(8) Filtration After harvesting and removal of samples for the safety tests prescribed in § 630.16(a), the pool shall be passed through sterile filters having a sufficiently small porosity to assure bacteriologically sterile filtrates.

§ 630.14 Reference strains.

The following reference viruses shall be obtained from the Office of Biologics Research and Review.
Reference Poliovirus, Live, Attenuated, Type 1, as a control for correlation of virus titers in tissue cultures.
Reference Poliovirus, Live, Attenuated, Type 2, as a control for correlation of virus titers in tissue cultures.
Reference Poliovirus, Live, Attenuated, Type 3, as a control for correlation of virus titers in tissue cultures.
Reference Attenuated Poliovirus, Type 1, as a control for correlation of monkey neurovirulence tests.

§ 630.15 Potency test.

The virus content expressed as infectivity titer/ml for cell cultures shall constitute the potency measurement. The accuracy and validity of the titration used to determine the concentration of live virus in the lot tested shall be confirmed by performing the titration with a Reference Poliovirus, Live, Attenuated of the appropriate type. The reference titration, when tested in parallel, shall be %n%n 0.5 log T21 T20 of its established titer, and shall not be used to adjust the titer of the lot under test.

§ 630.16 Test for safety.

(a) Tests prior to filtration Monovalent virus pools shall contain no demonstrable viable microbial agent other than the attenuated live poliovirus intended except for unavoidable bacteriophage. The vaccine shall be tested for the absence of adventitious and other infectious agents including polioviruses of other types or strains, simian agents Mycobacterium tuberculosis, pox virus, lymphocytic choriomeningitis virus, Echo viruses, Coxsackie viruses, and B virus. Testing of each monovalent pool shall include the following procedures:

(a)(1) Inoculation of rabbits A minimum of 100 ml. of each monovalent virus pool shall be tested by inoculation into at least 10 healthy rabbits, each weighing 1,500-2,500 grams. Each rabbit shall be injected intradermally in multiple sites, with a total of 1.0 ml. and subcutaneously with 9.0 ml., of the viral pool, and the animals observed for at least 3 weeks. Each rabbit that dies after the first 24 hours of the test or is sacrificed because of illness shall be necropsied and the brain and organs removed and examined. The virus pool may be used for poliovirus vaccine only if at least 80 percent of the rabbits remain healthy and survive the entire period and if all the rabbits used in the test fail to show lesions of any kind at the sites of inoculation and fail to show evidence of B virus or any other viral infection.

(a)(2) Inoculation of adult mice Each of at least 20 adult mice, each weighing 15-20 grams, shall be inoculated intraperitoneally with 0.5 ml. and intracerebrally with 0.03 ml. of each monovalent virus pool to be tested. The mice shall be observed for 21 days. Each mouse that dies after the first 24 hours of the test, or is sacrificed because of illness, shall be necropsied and examined for

evidence of viral infection by direct observation and subinoculation of appropriate tissue into at least five additional mice which shall be observed for 21 days. The monovalent virus pool may be used for poliovirus vaccine only if at least 80 percent of the mice remain healthy and survive the entire period and if all the mice used in the test fail to show evidence of lymphocytic choriomeningitis virus or other viral infection.

(a)(3) Inoculation of suckling mice Each of at least 20 suckling mice less than 24 hours old, shall be inoculated intracerebrally with 0.01 ml. and intraperitoneally with 0.1 ml. of the monovalent virus pool to be tested. The mice shall be observed daily for at least 14 days. Each mouse that dies after the first 24 hours of the test, or is sacrificed because of illness, shall be necropsied and all areas examined for evidence of viral infection. Such examination shall include subinoculation of appropriate tissue suspensions into an additional group of at least five suckling mice by the intracerebral and intraperitoneal routes and observed daily for 14 days. In addition, a blind passage shall be made of a single pool of the emulsified tissue (minus skin and viscera) of all mice surviving the original 14-day test. The virus pool under test is satisfactory for poliovirus vaccine only if at least 80 percent of the mice remain healthy and survive the entire period and if all the mice used in the test fail to show evidence of Coxsackie or other viral infection.

(a)(4) Inoculation of guinea pigs Each of at least five guinea pigs, each weighing 350-450 grams, shall be inoculated intracerebrally with 0.1 ml. and intraperitoneally with 5.0 ml. of the monovalent virus pool to be tested. The animals shall be observed for at least 42 days and daily rectal temperatures recorded for the last 3 weeks of the test. Each animal that dies after the first 24 hours of the test, or is sacrificed because of

illness, shall be necropsied and its tissues shall be examined both microscopically and culturally for evidence of tubercle bacilli, and by passage of tissue suspensions into at least three other guinea pigs by the intracerebral and intraperitoneal routes of inoculation for evidence of viral infection. If clinical signs suggest infection with lymphocytic choriomeningitis virus, serological tests shall be performed on blood samples of the test guinea pigs to confirm the clinical observations. Animals that die or are sacrificed during the first 3 weeks after inoculation with poliovirus shall be examined for infection with lymphocytic choriomeningitis virus. Animals that die in the final 3 weeks shall be examined both microscopically and culturally for Mycobacterium tuberculosis. The monovalent virus pool is satisfactory for poliovirus vaccine only if at least 80 percent of all animals remain healthy and survive the observation period and if all the animals used in the test fail to show evidence of infection with Mycobacterium tuberculosis, or any viral infection.

(a)(5) Inoculation of monkey kidney tissue cultures At least 500 doses or 50 ml., whichever represents a greater volume of virus, of each undiluted monovalent virus pool, or in equal proportions from individual harvests or subpools, shall be tested for simiam viruses in Macaca, and the same volume in Cercopithecus, monkey kidney tissue cultures, in a ratio of inoculum to medium of from 1:1 to 1:3, and with the area of surface growth of cells at least 3 square centimeters per milliliter of test inoculum, after neutralization of the poliovirus by high titer specific antiserum of nonprimate origin. The immunizing antigens used for the preparation of antisera shall be grown in a human tissue culture cell line. The cultures shall be observed for no less than 14 days. At the end of the observation period at least one subculture of fluid

from the Cercopithecus kidney cell culture shall be made in the same tissue culture system and the subculture shall be observed for at least 14 days. The monovalent virus pool is satisfactory for poliovirus vaccine only if all the tissue cultures fail to show evidence of the presence of simian viruses or any other viral infection.

(a)(6) Inoculation of human cell cultures At least 500 doses or 50 mL., whichever represents a greater volume of virus, taken from either a single monovalent pool, or in equal proportions from individual harvests or subpools, shall be tested in a ratio of inoculum to medium of 1:1 to 1:3, and with the area of surface growth of cells at least 3 square centimeters per milliliter of test inoculum, for the presence of measles virus in either (i) primary human amnion cells, (ii) primary human kidney cells, or (iii) any other cell system of comparable susceptibility to unmodified measles virus. The test material shall be neutralized with poliovirus antiserum of other than primate origin if the tissue culture cell system used is susceptible to poliovirus. The culture shall be observed for no less than 14 days. The monovalent virus pool is satisfactory for poliovirus vaccine only if all tissue cultures fail to show evidence of the presence of measles virus or any other viral infection.

(a)(7) Inoculation of a rabbit kidney tissue cultures At least 500 ml. of virus pool taken from either a single monvalent pool, or in equal proportions from individual harvests or subpools, shall be tested in a ratio of inoculum to medium of from 1:1 to 1:3, and with the area of surface growth of cells at least 3 square centimeters per milliliter of test inoculum, in primary rabbit kidney tissue culture preparations for evidence of B virus. The culture shall be observed for no less than 14 days. The monovalent virus pool is satisfactory for

poliovirus vaccine only if all tissue cultures fail to show evidence of the presence of B virus.

(b) Tests after filtration The following tests relating to safety shall be performed after the filtration process, on each monovalent virus pool or on each multiple thereof (monovalent lot):

(b)(1) Neurovirulence in monkeys Each monovalent virus pool or monovalent lot shall be tested in comparison with the Reference Attenuated Poliovirus for neurovirulence in Macaca monkeys by both the intrathalamic and intraspinal routes of injection. A preinjection serum sample obtained from each monkey must be shown to contain no neutralizing antibody in a dilution of 1:4 when tested against no more than 1,000 TCID T25 T20 of each of the three types of poliovirus. The neurovirulence tests are not valid unless the sample contains at least 10 [FN7.0] TCID T25 T20 per ml. when titrated in comparison with the Reference Poliovirus, Live, Attenuated of the appropriate type. All monkeys shall be observed for 17 to 21 days, under the supervision of a qualified pathologist, physician or veterinarian, and any evidence of physical abnormalities indicative of poliomyelitis or other viral infections shall be recorded.

(b)(1)(i) Intrathalamic inoculation Each of at least 30 monkeys shall be injected intracerebrally by placing 0.5 ml. of virus pool material into the thalamic region of each hemisphere. Comparative evaluations shall be made with the virus pool under test and the Reference Attenuated Poliovirus. Only monkeys that show evidence of inoculation into the thalamus shall be considered as having been injected satisfactorily. If on examination there is evidence of failure to inoculate virus pool material into the thalmus, additional monkeys may be

inoculated in order to reestablish the minimum number of 30 monkeys for the test.

(b)(1)(ii) Intraspinal inoculation Each of a group of at least five monkeys shall be injected intraspinally with 0.2 ml. of virus pool material containing at least 10 [FN7.0] TCID T25 T20 per ml. and each monkey in additional groups of at least five monkeys shall be injected intraspinally with 0.2 ml of a 1:1,000 and 1:10,000 dilution respectively, of the same virus pool material. Comparative evaluations shall be made with the virus pool under test and the reference material. Only monkeys that show microscopic evidence of inoculation into the gray matter of the lumbar cord shall be considered as having been injected satisfactorily. If on examination there is evidence of failure to inoculate intraspinally, additional animals may be inoculated in order to reestablish the minimum number of five animals per group.

(b)(1)(iii) Determination of neurovirulence At the conclusion of the observation period comparative histopathological examinations shall be made of the lumbar cord, cervical cord, lower medulla, upper medulla, mesencephalon and motor cortex of each monkey in the groups injected with virus under test and those injected with the Reference Attenuated Poliovirus, except that for animals dying during the test period, these examinations shall be made immediately after death. If at least 60 percent of the animals of a group survive 48 hours after inoculation, those animals which did not survive may be replaced by an equal number of animals tested as prescribed in paragraph (b)(1) of this section. If less than 60 percent of the animals of a group survive 48 hours after inoculation, the test must be repeated. At the conclusion of the observation the animals shall be examined to ascertain whether the

distribution and histological nature of the lesions are characteristics of poliovirus infection. A comparative evaluation shall be made of the evidence of neurovirulence of the virus under test and the Reference Attenuated Poliovirus with respect to (a) the number of animals showing lesions characteristic of poliovirus infection, (b) the number of animals showing lesions other than those characteristic of poliovirus infection, (c) the severity of the lesions, (d) the degree of dissemination of the lesions, and (e) the rate of occurrence of paralysis not attributable to the mechanical injury resulting from inoculation trauma. The virus pool under test is satisfactory for poliovirus vaccine only if at least 80 percent of the animals in each group survive the observation period and if a comparative analysis of the test results demonstrate that the neurovirulence of the test virus pool does not exceed that of the Reference Attenuated Poliovirus.

(b)(1)(iv) Test with Reference Attenuated Poliovirus The Reference Attenuated Poliovirus shall be tested as prescribed in paragraph (b)(1)(i) and (ii) of this section at least once for every 10 production lots of vaccine, except that the interval between the test of the reference and the test of any lot of vaccine shall not be greater than 3 months. The test procedure shall be considered acceptable only if lesions of poliomyelitis are seen in monkeys inoculated with the reference material at a frequency statistically compatible with all previous tests with this preparation.

(b)(2) Test for virus titer The concentration of living virus in each monovalent virus pool or lot expressed as infectivity titer/ml for cell cultures shall be determined using the Reference Poliovirus, Live, Attenuated of the same type as a control. A titration of the monovalent virus pool or lot shall not constitute a valid test unless

the titration of the reference virus when tested in parallel is within % n%n 0.5 log T21 T20 of its established titer. The titration of the parallel reference is intended to validate the test system and shall not be used to adjust the titer of the lot under test.

(b)(3) Tests for In Vitro Markers A test shall be performed on each monovalent virus pool or each monovalent lot resulting therefrom, using the rct/40 Marker. A second test shall be performed using the d Marker or another marker method shown to be of value in identification of the attenuated strain. The test results shall demonstrate that the virus under test and the seed virus have substantially the same marker characteristics.

(b)(3)(i) rct/40 Marker Attenuated strains which grow readily at 40 degrees C. (%n%n 0.5 degrees C.) are classified as rct/40 positive (+) in contrast to the rct/40 negative (-) strains which show an increased growth of at least 100,000 fold at 36 degrees C. over that obtained at 40 degrees C. Comparative determinations shall be made in either tube or bottle cultures.

(b)(3)(ii) d Marker Attenuated strains which grow readily at low concentrations of bicarbonate under agar are classified as d positive (+) in contrast to the d negative (-) strains which exhibit delayed growth under the same conditions. The cultures shall be grown in a 36 degrees C. incubator either in stoppered bottles of in plates in an environment of 5 percent CO T22 in air.

§ 630.17 General requirements.

(a) Final container sterility test The final container sterility test need not be performed provided aseptic techniques are used in the filling process.

(b) Consistency of manufacture No lot of vaccine shall be released unless each monovalent pool contained therein is one of a series of five consecutive pools of the same type, each pool having been manufactured by the same procedures, and each having met the criteria of neurovirulence for monkeys prescribed in § 630.16(b)(1), and of in vitro markers prescribed in § 630.16(b)(3).

(c) Dose Each monovalent vaccine shall be constituted to have an infectivity titer of not less than 10 [FN5.3] nor greater than 10 [FN6.0] per human dose. The human dose of vaccines containing all three virus types shall be constituted to have infectivity titers in the final container material of 10 [FN5.4] to 10 [FN6.4] for Type I, 10 [FN4.5] to 10 [FN5.5] for Type II, and 10 [FN5.2] to 10 [FN6.2] for Type III.

(d) Labeling In addition to the items required by other applicable labeling provisions of this part, the final container label shall bear a statement indicating that liquid vaccine may not be used for more than 7 days after opening the container. Labeling may include a statement indicating that for frozen vaccine a maximum of 10 freeze-thaw cycles is permissible provided the total cumulative duration of thaw does not exceed 24 hours, and provided the temperature does not exceed 8 degrees C. during the periods of thaw.

(e) Samples and protocols. For each lot of vaccine, the following materials shall be submitted to the Director, Office of Biologics Research and Review, Food and Drug Administration, 8800 Rockville Pike, Bethesda, MD 20892:

(e)(1) A protocol which consists of a summary of the history of manufacture of each lot including all results

of each test for which test results are requested by the Director, Office of Biologics Research and Review.

(e)(2) A 200-milliliter bulk sample of each final monovalent pool having a virus titer of no less than 10 [FN7.5] TCID50 per milliliter, except that if the titer is greater, a correspondingly smaller volume may be submitted.

(e)(3) A total of no less than 200 doses or no less than six final containers, whichever is the larger amount.

EXTRACTS FROM CYANAMID SUBMITTALS TO
FDA Docket No. 86N-0027

September 29, 1987 "Further Lederle Comments On Proposed Rule, 'Additional Standards For Viral Vaccine: Poliovirus Vaccine -- Live Oral,'" FDA Docket No. 86N-0027

Since live-oral poliovirus vaccine (OPV) first began to be administered in this country, the safety and quality of the vaccine has been ensured by a requirement of "consistency of manufacture." In its May 5, 1986 proposal to revise standards for OPV, the Food and Drug Administration (FDA) eliminated this requirement. 51 Fed.Reg. 16620, 16627-28 (May 5, 1986). On the basis of its extensive experience in vaccine manufacturing, Lederle Laboratories strongly disagreed with the elimination of the "consistency of manufacture" requirement when filing its first set of comments concerning the FDA proposal. [FN1] Recently developed scientific data confirm Lederle's original position on this issue. These comments address Lederle's concerns and the new supporting scientific information.

At page 1 (footnote omitted).

I. Current Requirements

At present, FDA regulations require that:

> No lot of vaccine shall be released unless each monovalent pool contained therein is one of a series of five consecutive pools of the same type, each pool having been manufactured by the same procedures, and each having met the criteria of

> neurovirulence f or monkeys and of in vitro markers . . . .

21 C.F.R. §630.17(b). This requirement, designed to ensure quality and consistency in the manufacturing process, has been a vital part of FDA's regulatory scheme for vaccine licensing from the 1960's, when OPV was first approved.

The significance of the consistency criteria is reflected in regulatory action taken by FDA in 1984. At that time, the agency issued a final rule eliminating the requirement of five consecutive lots in clinical trials. As part of its justification for this action, FDA relied on the continued existence of the consistency of manufacture requirement:

> The agency emphasizes that this amendment will not affect the regulatory requirements for the consistency of manufacture of licensed oral poliovirus vaccine for commercial use. FDA will continue to impose the requirements in §630.17(b) for the release of individual lots of vaccine. These requirements include the requirement that each lot be one of five consecutive lots that have been manufactured satisfactorily.

49 Fed.Reg. 23004, 23005 (June 1, 1984). Thus, as recently as 1984, FDA clearly regarded the consistency of manufacture requirement. as an important safeguard in the manufacturing process for OPV.

Id. at 2-3.

II. FDA Proposal

In proposing to eliminate the consistency of manufacture requirement, FDA admitted that "[w]hen these additional standards were promulgated originally, FDA was concerned that the failure of a lot of poliovirus vaccine to meet the standards for acceptable neurovirulence could be related to a deficiency in the manufacturing process." 51 Fed.Reg. 61627. However, FDA went on to state that it "has now determined that failure of the neurovirulence test in monkeys is a random event related to the genetic instability of the seed virus which may result in a slight increase in neurovirulence." Id.

As a result of this "determination" that the consistency of manufacture requirement has become superfluous once a seed is qualified, the agency proposes to rely solely on a new provision designed to disqualify defective seed viruses. [FN2]

[FN2] The new provision regarding seed viruses, proposed to be located at 21 C.F.R. §630.10(c)(5), states:

> The use of the seed virus may continue provided that the frequency of monovalent virus pools produced with it which fail to meet the criteria of neurovirulence for monkeys prescribed in 6630.16(b)(1)(ii) is not greater than predicted on the basis of comparison with the corresponding reference preparation. If the frequency

> of monovalent virus pools produced with the same seed virus which fail to meet the criteria of neurovirulence for monkeys prescribed in §630.16(b)(1)(ii) is greater than the predicted 1 percent on the basis of the 99 percent fiduciary one-sided upper limit, that seed virus shall be disqualified for further use in vaccine production.
>
> 51 Fed. Reg. 16629 [end FN2]

FDA states that this provision regarding seed viruses "will assure the continued manufacture of safe vaccine" so that "the consistency of manufacture requirements in §630.17(b) are inappropriate and no longer necessary." In addition, FDA asserted "that the proposed rule will assure the continued low neurovirulence of oral poliovirus vaccine while not requiring interruption of trivalent vaccine production each time a single monovalent lot fails the neurovirulence test." 51 Fed.Reg. 16628.

In its regulatory proposal, FDA cites no empirical evidence or scientific data supporting its conclusion that the consistency of manufacture requirement is no longer necessary or that the safety of the vaccine will be assured by use of the alternative approach set forth in the proposal. Moreover, FDA has identified no manufacturing quality control system from another regulatory authority on which it relies as a model in eliminating the consistency requirement.

Ironically, the only model cited by FDA for the proposed changes in the regulations is the WHO guidelines, which, contrary to FDA's position, strongly endorse the necessity for consistency requirements in production: "The most important concerning the safety of a biological substance is given by consistency of production, which is complimentary to the tests applied to the final filled material. [FN3 omitted]

* * *

Thus, like current U.S. regulations, the WHO guidelines expressly call for production controls to ensure consistency of manufacture in addition to neurovirulence testing. Surprisingly, FDA appears to have ignored both the long U.S. experience of safe vaccines based on a sound consistency requirement and the recommendation of WHO as to the need for such a requirement. In short, the agency has proposed the complete elimination of a quality control system which has ensured safe vaccine in this country for 25 years and the adoption in its place of a system which is untested and has no scientific or other basis, at least in so far-as is reflected in the rulemaking record.

Id. at 3-6.

III. Applicable Legal Standard

* * *

In this rulemaking, FDA has proposed to eliminate a requirement designed to ensure the consistency and quality of manufacturing processes -- a requirement which has been a part of the vaccine regulatory scheme for many years. Applicable law compels the agency to set forth a substantial rationale, based on accumulated scientific or other factual data, in

order to justify such a drastic shift in regulatory policy. Far from meeting this standard, FDA has announced in a conclusory fashion that the consistency of manufacture requirement is no longer appropriate or necessary. This fails to meet even minimum standards for rulemaking under the APA.

IV. Flaws in FDA Approach

FDA's proposal to eliminate the consistency of manufacture requirement and substitute for it a seed disqualification provision is based on two faulty assumptions: first, that failures in the neurovirulence test are necessarily the result of deficiency in the seed virus; and second, that checks on the consistency and reliability of manufacturing processes are no longer required for the production of safe vaccines.

Id. at 6-7.

* * *

Even more flawed is FDA's second assumption, that the manufacturing processes employed by producers of OPV make little difference in the safety of the vaccine. Production seeds for poliovirus vaccine are not homogenous [sic]. While the predominant population in a qualified seed virus will demonstrate genetic stability, even slight deviation in the manufacturing process could create selective conditions favoring replication of less attenuated subpopulations of virus that could exist in the seed. In turn, the distribution of such subpopulations of virus in the particular monopool could be affected.

Id. at 8 (emphasis supplied).

* * *

The heterogeneity of even the best vaccine seeds is reflected in the observation of Lederle scientists and other that the published cDNA sequences for Sabin 3 seed viruses sequenced in the United Kingdom and in Japan are different from one another and are clearly distinguishable from the RNA sequence of the U.S. version of the Sabin 3 virus strain in the 5' noncoding region of the poliovirus genome. All three of these viruses were derived from the Sabin 3 strain so that the observed differences are likely to have resulted from differences in vaccine manufacture.

Id. at 9.

Among the variables in the manufacturing process which might influence the neurovirulence and therefore the safety of the vaccine are the following:

* * *

> Cell Substrate -- The nature of the cell substrate used for cultivation of the vaccine can influence neurovirulence. FDA itself has noted the possibility of excessive neurovirulence in the case of multiple passages of the virus in human cells. **Lederle studies suggest that even a single passage through human cells may be associated with increases in neurovirulence**.

Id. at 10 (emphasis supplied, footnotes omitted).

> Acidity/Alkalinity -- Sabin's strains require a high level of alkalinity or high pH. In vitro studies have demonstrated that populations of virus can experience shifts in phenotypic properties when Sabin strains are grown at a low pH. These shifts

> in phenotypic properties in turn relate to conditions associated with excessive levels of neurovirulence.

* * *

While all of these factors are intended to be controlled in the manufacturing process, it is possible that even slight variations in one or more of them could cause failure in the neurovirulence test. Furthermore, because all the factors affecting neurovirulence are not completely known, *other variables could also play a role in creating an excessively neurovirulent vaccine monopool. It seems evident that the neurovirulence of the vaccine may be determined not only by the genetic stability of the seed virus but also by the manufacturing process which creates the vaccine.*

Id. at 9-11 (emphasis supplied.)